



Ottawa Hull K1A 0C9

(21) (A1) 2,156,729  
(86) 1994/03/02  
(43) 1994/09/15

(51) Int.Cl. <sup>6</sup> C07D 213/74; C07D 401/12; C07D 405/12; C07D 409/12;  
C07D 413/12; C07D 417/12; A61K 31/395

(19) (CA) APPLICATION FOR CANADIAN PATENT (12)

(54) New 4-Aminopyridines, Processes for Their Production as  
Well as Pharmaceutical Agents Containing These Compounds

(72) Heck, Reinhard - Germany (Federal Republic of) ;  
Leinert, Herbert - Germany (Federal Republic of) ;  
Poll, Thomas - Germany (Federal Republic of) ;  
Stegmeier, Karlheinz - Germany (Federal Republic of) ;  
Von Der Saal, Wolfgang - Germany (Federal Republic of) ;  
Michel, Helmut - Germany (Federal Republic of) ;

(71) Boehringer Mannheim GmbH - Germany (Federal Republic of)  
;

(30) (DE) P 43 06 506.6 1993/03/03  
(US) P 43 12 966.8 1993/04/21

(57) 15 Claims

Notice: This application is as filed and may therefore contain an  
incomplete specification.

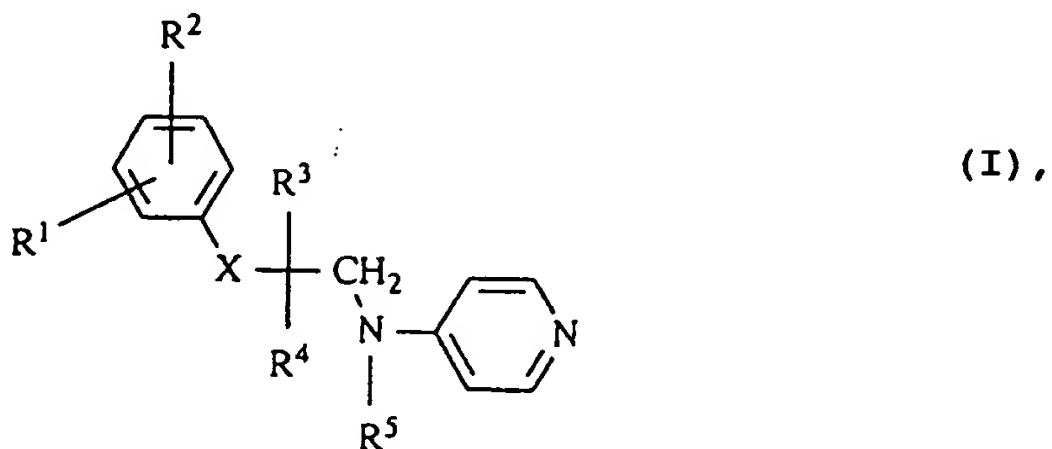


2156729

Boehringer Mannheim GmbH  
3790/OA/

**New 4-aminopyridines, processes for their production as well as pharmaceutical agents containing these compounds**

The invention concerns new 4-aminopyridines of the general formula I



in which

$R^1$  denotes a  $R^6$ -SO-NR<sup>7</sup>-,  $R^6$ -SO<sub>2</sub>-NR<sup>7</sup>-,  $R^6$ -NR<sup>7</sup>-SO-,  $R^6$ -NR<sup>7</sup>-SO<sub>2</sub>-,  $R^6$ -SO-O-,  $R^6$ -SO<sub>2</sub>-O-,  $R^6$ -O-SO- or  $R^6$ -O-SO<sub>2</sub>- group,

$R^2$  denotes a hydrogen or halogen atom, a cyano, alkyl, alkoxy or haloalkyl group,

X denotes an oxygen atom, a sulphur atom or a NH group,

$R^3$  and  $R^4$  are the same or different and denote hydrogen atoms or alkyl groups,

- R<sup>5</sup> denotes a hydrogen atom, an alkyl group or an aralkyl group,
- R<sup>6</sup> denotes an alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroarylalkyl group in which the aryl or heteroaryl residues can be substituted once or several times by nitro, halogen, nitrile, hydroxy, carboxy, alkoxycarbonyl, alkenyloxycarbonyl, alkinyloxycarbonyl, aralkoxycarbonyl, alkyl, cycloalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxy, alkenyloxy, alkinyloxy, aralkyloxy, cyanoalkyloxy, alkylthio, alkylsulfinyl, alkylsulfonyl, amino, alkylamino, dialkylamino, aralkylamino, di-aralkylamino, alkylsulfonylamino, alkylcarbamoylamino, formylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl or by one or several of the groups  $-Y-CO_2R^8$ ,  $-S-Y-CO_2R^8$ ,  $-O-Y-CO_2R^8$ ,  $-NH-Y-CO_2R^8$ ,  $-S-Y-CONR^8R^9$ ,  $-O-Y-CO-NR^8R^9$  or  $-NH-Y-CONR^8R^9$  in which the alkyl, alkenyl or alkynyl fragments can be substituted once or several times by halogen, hydroxy, alkoxy, alkylcarbonyloxy, amino or carboxy groups,
- R<sup>7</sup> denotes a hydrogen atom, an alkyl, cycloalkyl, alkenyl or alkynyl residue wherein these residues can be substituted once or several times by halogen, hydroxy, alkoxy, amino, alkylamino, dialkylamino, carboxy, alkylcarbonyl or alkoxy-carbonyl, or denote an alkoxycarbonyl, cyanoalkyl, heteroaryl, aryl, aralkyl or heteroarylalkyl group in which case the aryl or heteroaryl residue can be substituted once or several times by halogen, nitrile, alkyl, alkenyl, alkynyl, trifluoromethyl, alkoxy, alkenyloxy, alkinyloxy, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkoxy, trifluoro-

methoxy, hydroxy, carboxy, hydroxyalkyl, carboxy-alkyl, alkoxycarbonyl, amino, alkylamino, dialkyl-amino, alkylsulfonylamino, alkylcarbonylamino, formylamino, aminocarbonyl or phenyl, or denotes a  $-Y-CO_2R^8$  or  $-Y-CONR^8R^9$  group,

Y denotes a linear or branched alkylene chain,

$R^8$  and  $R^9$  are the same or different and denote hydrogen atoms, aralkyl, cycloalkyl or alkyl groups, which can be substituted once or several times by halogen, hydroxy, alkoxy, alkylcarbonyloxy, amine or carboxy, or  $R^8$  and  $R^9$  together with the N atom to which they are bound, form a saturated ring which can contain an additional oxygen, sulphur or nitrogen atom,

as well as hydrates, solvates and physiologically tolerated salts thereof. The invention also concerns the optically active forms, racemates and mixtures of diastereomers of these compounds.

In addition the invention also concerns processes for the production of the above-mentioned compounds, pharmaceutical agents that contain such compounds as well as the use of these compounds in the production of pharmaceutical agents.

The aminopyridines of the general formula I, their solvates and their salts inhibit thrombin-induced coagulation of fibrinogen in blood as well as thrombin-induced aggregation of blood platelets. Thus they prevent formation of hyaline thrombi and platelet-rich thrombi and can be used to combat and prevent diseases

such as thrombosis, apoplexy, coronary infarction, inflammations and arteriosclerosis. Furthermore, these compounds have an effect on tumour cells and prevent formation of metastases. As a result they can be used as anti-tumour agents.

Thrombin, the last enzyme of the coagulation cascade, cleaves fibrinogen to form fibrin which is cross-linked by factor XIIIa and becomes an insoluble gel which forms the matrix for a thrombus. Thrombin activates platelet aggregation by proteolysis of its receptor on the blood platelets and in this way also contributes to thrombus formation. When a blood vessel is damaged these processes are necessary in order to stop bleeding. No measurable thrombin concentrations are present in blood plasma under normal circumstances. Increases in the thrombin concentration can lead to the formation of thrombi and hence to thromboembolic diseases which occur very frequently and above all in industrial countries.

Thrombin in plasma is kept ready in the form of prothrombin and is released from it by factor Xa. Thrombin activates factors V, VIII and XI by which means factor X is then converted into factor Xa. By this means thrombin catalyzes its own release which is why very rapid increases in thrombin concentrations can occur.

Thrombin inhibitors can therefore inhibit the release of thrombin, the platelet-induced and plasmatic blood coagulation.

There is a whole series of serine proteases apart from thrombin that cleave peptide substrates next to a basic amino acid. In order to limit side-effects, the thrombin

inhibitors should be selective i.e. they should inhibit other serine proteases only slightly or not at all. Trypsin in particular being the least specific serine protease, can be easily inhibited by the various inhibitors. Trypsin inhibition can lead to pancreatic stimulation and to pancreatic hypertrophy (J.D. Geratz, Am. J. Physiol. 216, (1969) p. 812).

Plasma contains the protein plasminogen which is converted into plasmin by activators. Plasmin is a proteolytic enzyme whose activity is similar to that of trypsin. It serves to dissolve thrombi by degrading fibrin. Inhibition of plasmin would thus have the opposite effect to that which one would like to achieve by inhibiting thrombin.

Synthetic thrombin inhibitors have already been known for a long time. Substances of the (D)-Phe-Pro-Arg type were synthesized from fibrinogen the natural substrate of thrombin. Such tripeptides imitate the amino acid sequence before the cleavage site on fibrinogen. In order to obtain good inhibitors the carboxylate group of the arginine was changed in such a way that the hydroxy group of serine 195 in the active site of thrombin can react with it. This can for example be achieved by replacing the carboxylate group by an aldehyde group. Corresponding (D)-Phe-Pro-arginals are described in the Patent Application EP-A 185390.

Benzamidine, a known trypsin inhibitor, was used as the basis for a second type of thrombin inhibitor. The inhibitors obtained in this way do not only differ from the (D)-Phe-Pro-Arg types in their chemical structure but also in the way they inhibit: serine 195 of thrombin

does not bind to these inhibitors. This clearly follows from X-ray examinations of the structure (W. Bode, D. Turk, J. Stürzebecher, Eur. J. Biochem. 193, 175-182 (1990)).  $N\alpha$ -(2-naphthylsulfonylglycyl)-4-amidino-(R,S)-phenylalanine-piperidide ("NAPAP", DD 235866) belongs to this second class of thrombin inhibitors.

It was now surprisingly found that compounds of the general formula I which do not have any structural features in common with known thrombin inhibitors, are selective thrombin inhibitors.

The alkyl or alkoxy fragments mentioned in the definitions of  $R^1 - R^9$  contain 1-6 carbon atoms wherein these fragments can be straight-chained or branched. The same applies to the corresponding alkenyl or alkynyl fragments. Cycloalkyl groups are rings with three to seven carbon atoms. In the case of a haloalkyl or haloalkoxy group, the alkyl or alkoxy group can be substituted once, twice or three times by halogen. A trifluoromethyl or trifluoromethoxy group preferably comes into consideration in the case of groups substituted three times by halogen. In all cases halogen denotes fluorine, chlorine, bromine or iodine. Aralkyl and aralkoxy groups are preferably understood as a benzyl or benzyloxy group. In those cases in which the stated groups can be substituted once or several times, a single, double or triple substitution comes into particular consideration. In the case of the six-membered rings in aryl or heteroaryl groups, the substituents can independently be in the ortho, meta or para position.

If one of the substituents  $R^2 - R^9$  in the general

formula I denotes an alkyl group, or  $R^6$  denotes an aryl or heteroaryl group substituted by one or several alkyl groups, then the alkyl groups are to be understood as straight-chained or branched alkyl groups with 1 to 6 carbon atoms and preferably a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.butyl, pentyl and hexyl group. The halogen atoms as substituents on the alkyl groups are understood as fluorine, chlorine, bromine or iodine and preferably fluorine and chlorine. The trifluoromethyl, chloromethyl, 2-chloroethyl and 3-chloropropyl group are preferred. If the alkyl groups are substituted by hydroxy groups, then the hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 1,2-dihydroxyethyl and 2,3-dihydroxypropyl group are preferred. If the alkyl groups are substituted by alkoxy groups, then the methoxymethyl, ethoxymethyl, methoxyethyl and ethoxyethyl group are preferred. If the alkyl groups are substituted by amino groups, then the aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl and 5-aminopentyl group are preferred. If the alkyl groups are substituted by carboxy groups, then the carboxymethyl, 1-carboxyethyl, 2-carboxyethyl and 2-methyl-1-carboxyethyl group are particularly preferred.

If  $R^6$ ,  $R^7$ ,  $R^8$  or  $R^9$  in the general formula I denote a cycloalkyl group or if  $R^6$  denotes an aryl or heteroaryl group substituted with a cycloalkyl group, then the cycloalkyl groups are to be understood as rings with 3 to 7 members and preferably a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl group. In all cases the cycloalkyl group can also be linked via an alkyl group so that a cycloalkyl-alkyl group results as a substituent. In this case a cyclopropylmethyl or cyclohexylmethyl group are particularly preferred.

If  $R^6$  in the general formula I denotes an aryl or heteroaryl group substituted with an alkenyl residue or if  $R^7$  denotes an alkenyl residue, then these are to be understood as straight-chained or branched residues with 3 to 6 members and preferably an allyl, butenyl or isobutenyl residue.

If  $R^6$  in the general formula I denotes an aryl or heteroaryl group substituted with an alkynyl residue or if  $R^7$  denotes an alkynyl residue, then these are to be understood as straight-chained or branched residues with 3 to 6 members and preferably a propargyl residue.

If  $R^6$  in the general formula I denotes an aryl or heteroaryl group substituted with an alkoxycarbonyl, alkenyloxycarbonyl or alkynyloxycarbonyl residue, then these are to be understood as straight-chained or branched residues with 2 to 6 carbon atoms and preferably a methoxycarbonyl, ethoxycarbonyl or allyloxycarbonyl group.

If  $R^6$  in the general formula I denotes an aryl or heteroaryl group substituted with an alkoxy residue, then this is to be understood as a straight-chained or branched residue with 1 to 6 carbon atoms and preferably a methoxy, ethoxy, propyloxy, butyloxy or pentyloxy group. If the alkoxy groups are substituted by hydroxy groups, then a 2-hydroxyethoxy, 3-hydroxypropyloxy and 2,3-dihydroxypropyloxy group are preferred. If the alkoxy groups are substituted by alkoxy groups, then a methoxyethoxy or ethoxyethoxy group is preferred. If the alkoxy groups are substituted by amino groups, then a 2-aminoethoxy and 3-aminopropyloxy group are preferred.

If  $R^6$  in the general formula I denotes an aryl or heteroaryl group substituted with an alkenyloxy residue, then this is to be understood as a straight-chained or branched residue with 3 to 6 carbon atoms and preferably an allyloxy group.

If  $R^6$  in the general formula I denotes an aryl or heteroaryl group substituted with an alkynyloxy residue, then this is to be understood as a straight-chained or branched residue with 1 to 6 carbon atoms and preferably a propargyloxy group.

If  $R^6$  in the general formula I denotes an aryl or heteroaryl group substituted by an alkylthio, alkylsulfinyl or alkylsulfonyl residue, then these are to be understood as straight-chained or branched residues with 1 to 6 carbon atoms and preferably a methylthio, methylsulfinyl or methylsulfonyl group.

If  $R^6$  in the general formula I denotes an aryl or heteroaryl group substituted with an alkylamino or dialkylamino residue, then these are to be understood as straight-chained or branched residues with 1 to 6 carbon atoms and preferably a methylamino, dimethylamino or diethylamino group.

If  $R^6$  in the general formula I denotes an aryl or heteroaryl group substituted with an alkylsulfonylamino residue, then this is to be understood as a straight-chained or branched residue with 1 to 6 carbon atoms and preferably a methylsulfonylamino group.

If  $R^6$  in the general formula I denotes an aryl or heteroaryl group substituted with an alkylcarbonylamino

residue, then this is to be understood as a straight-chained or branched residue with 1 to 6 carbon atoms and preferably an acetylamino group.

If  $R^6$  in the general formula I denotes an aryl or heteroaryl group substituted with an alkylaminocarbonyl or dialkylaminocarbonyl residue, then these are to be understood as straight-chained or branched residues with 1 to 6 carbon atoms and preferably a methylaminocarbonyl, dimethylaminocarbonyl or diethylaminocarbonyl group.

The benzyl group is particularly preferred among the aralkyl groups for  $R^6$  and  $R^7$ .

The aryl residues  $R^6$  or  $R^7$ , either alone or linked to an alkyl chain, are to be understood as aromatic hydrocarbons with 6-14 C atoms, in particular a phenyl, biphenyl, naphthyl, tetrahydronaphthyl, indanyl or fluorenyl residue.

As heteroaryl radical for  $R^6$  are to be understood mono, bi- and tricyclic aromatics with heteroatoms, such as nitrogen, oxygen and sulphur, for example furan, thiophene, pyrrole, oxazole, isoxazole, thiazole, isothiazole, imidazole, pyrazole, triazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazine, tetrazine, benzothiophene, dibenzothiophene, benzimidazole, carbazole, benzofuran, benzofurazane, benzo-2.1.3-thiadiazole, quinoline, isoquinoline, quinazoline.

By the alkylene group Y in the general formula I one understands linear or branched hydrocarbon chains with 1 to 6 carbon atoms, preferably methylene, ethylene or propylene group.

If the substituents  $R^8$  and  $R^9$ , together with the nitrogen atom to which they are attached, form a ring, then there are to be understood thereunder rings with 4 to 7 members, especially the pyrrolidine, the piperidine and the homopiperidine ring. If this cycle contains additional heteroatoms, then thereunder are preferred the morpholine, thiomorpholine and the piperazine ring.

The radical  $R^2$  on the phenyl ring of the general formula I can stand in any desired positions to the fragment X (oxygen atom or NH group). However, especially preferred is an arrangement in which all three substituents of the phenyl ring of the general formula I stand in meta-position to one another.

$R^1$  signifies especially the groups  $R^6-SO_2-NR^7-$ ,  $R^6-NR^7-SO_2-$ ,  $R^6-SO_2-O-$  or  $R^6-O-SO_2-$ .

$R^2$  signifies especially a hydrogen, chlorine or bromine atom or a  $C_1-C_6$ -alkyl group, such as e.g. a methyl or ethyl group, or a  $C_1-C_6$ -alkoxy group, such as e.g. the methoxy group, or the trifluoromethyl group.

X is especially an oxygen atom or the NH group.

$R^3$  and  $R^4$  can be the same or different and preferably represent hydrogen atoms or  $C_1-C_6$ -alkyl group, especially hydrogen atoms or the methyl group.

$R^5$  is in particular a hydrogen atom, a  $C_1$ - $C_6$  alkyl group (such as a methyl group) or a benzyl group.

$R^6$  is in particular a  $C_1$ - $C_6$  alkyl group (such as an isopropyl group), a  $C_3$ - $C_7$  cycloalkyl group (such as a cyclopentyl or cyclohexyl group), a phenyl group substituted once or several times by fluorine, chlorine,  $C_1$ - $C_6$  alkyl (such as e.g. methyl, ethyl, tert.butyl),  $C_1$ - $C_6$  alkoxy (such as methoxy), nitro, amino, hydroxy, carboxy, benzyloxycarbonyl,  $C_1$ - $C_6$ -alkoxycarbonyl (such as e.g. methoxycarbonyl), trifluoromethyl or the group  $-O-Y-CO_2R^8$ ; a naphthyl, tetrahydronaphthyl, biphenyl or indanyl group, a thienyl, pyrazolyl or pyridyl group, a benzthienyl or benzothiadiazinyl group or a benzyl group.

$R^7$  is in particular a hydrogen atom, a  $C_1$ - $C_6$  alkyl or  $C_2$ - $C_6$  alkenyl group (such as e.g. a methyl, ethyl, n-propyl, allyl, i-propyl group) or an aralkyl group (such as e.g. a benzyl group), a  $C_1$ - $C_6$  alkoxycarbonyl group (such as e.g. an ethoxycarbonyl group), a cyanoalkyl group (such as e.g. a cyanomethyl group), a hydroxyalkyl group (such as e.g. a hydroxyethyl or dihydroxypropyl group), or an aminoalkyl group (such as e.g. an aminoethyl group), a  $-Y-COR^8$  group or a  $-Y-CONR^8R^9$  group.

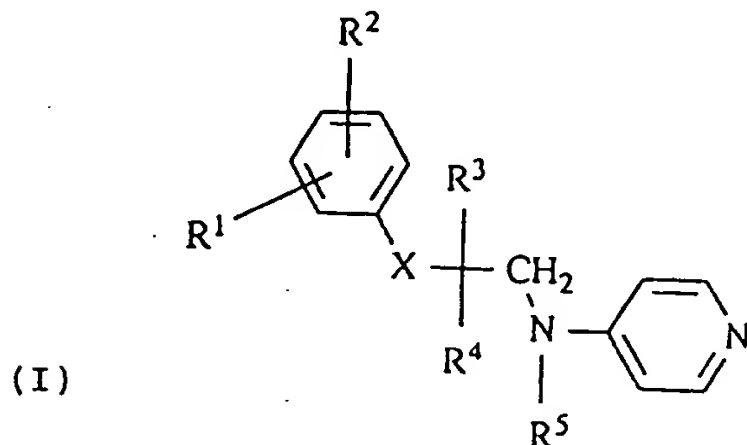
$Y$  is in particular a methylene, propylene, butylene or pentylene group.

$R^8$  is in particular a hydrogen atom or an alkyl group (such as e.g. a methyl or ethyl group), a hydroxyalkyl group (such as e.g. a hydroxyethyl, hydroxypropyl or dihydroxypropyl group) or an aminoalkyl group (such as

e.g. an aminoethyl group).

$R^9$  is in particular a hydrogen atom or an alkyl group (such as e.g. a methyl group).

Preferred are compounds of the general formula I,

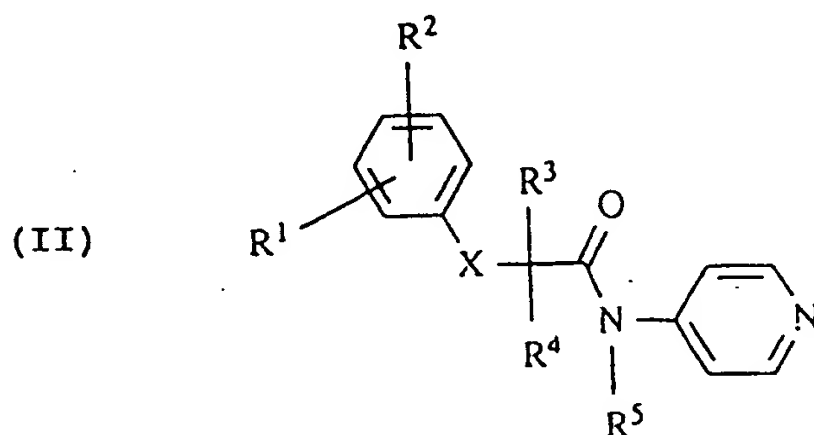


in which  $R^1$  signifies the groups  $R^6-SO_2-NR^7-$ ,  $R^6-NR^7-SO_2-$ ,  $R^6-SO_2-O-$  or  $R^6-O-SO_2-$ ,  $R^2$  signifies a hydrogen, chlorine or bromine atom, a methyl, ethyl, methoxy or the trifluoromethyl group,  $X$  signifies an oxygen atom or the NH group,  $R^3$  and  $R^4$  are the same or different and signify hydrogen atoms or methyl groups,  $R^5$  signifies a hydrogen atom, a methyl or benzyl group,  $R^6$  signifies an isopropyl, cyclopentyl or cyclohexyl group, phenyl group unsubstituted or substituted one or more times by fluorine, chlorine, methyl, ethyl, tert.-butyl, methoxy, nitro, amino hydroxyl, carboxyl benzyloxycarbonyl, methoxycarbonyl, trifluoromethyl or the group  $-O-Y-CO_2R^8$ , a naphthyl, tetrahydronaphthyl, biphenyl or indanyl group, a thienyl, pyrazolyl or pyridyl group, a benzthienyl or benzothiadiazinyl group or the benzyl group,  $R^7$  signifies a hydrogen atom, a methyl, ethyl, n-propyl, allyl, i-propyl or a benzyl group, an ethoxy carbonyl, hydroxyethyl, dihydroxypropyl, cyanomethyl or aminoethyl group, a group  $-Y-COR^8$  or a group  $-Y-CONR^8R^9$ ,  $Y$  signifies a

methylene, propylene, butylene or pentylene group,  $R^8$  signifies a hydrogen atom or a methyl, ethyl, hydroxyethyl, hydroxypropyl, dihydroxypropyl or aminoethyl group,  $R^9$  signifies a hydrogen atom or a methyl group.

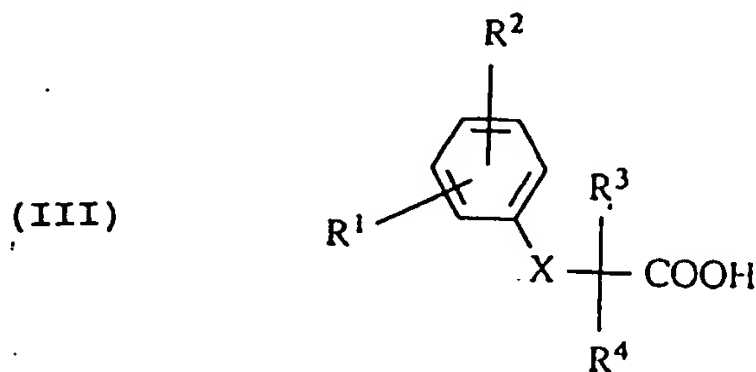
The preparation of compounds of the general formula I takes place according to per se known processes.

One starts from the compounds of the general formula II,



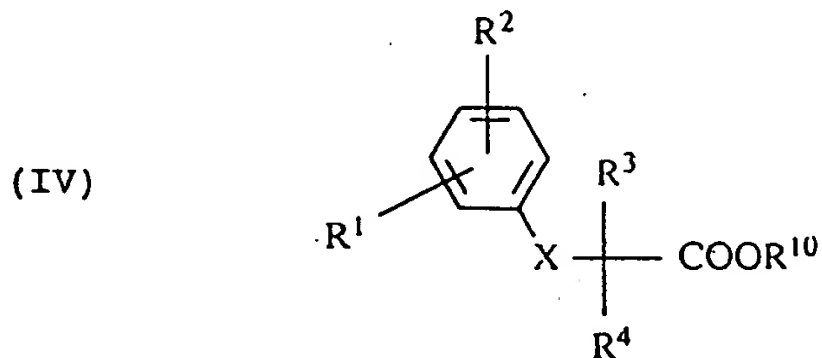
which one reduces according to conventional processes. As reducing agent, there come into consideration complex boron and aluminium hydrides, boron hydride complexes, aluminium hydride, which one prepares in situ by reaction of  $LiAlH_4$  with  $AlCl_3$  or  $H_2SO_4$ , or a mixture of  $AlCl_3$  and  $NaBH_4$ .

One prepares compounds of the general formula II by reaction of compounds of the general formula III



with 4-aminopyridine, the amino N-atom of which carries the radical  $R^5$ . This reaction takes place by reaction of equimolar amounts of the 4-aminopyridine and of the carboxylic acid of the general formula III in the presence of a water-removing agent, such as polyphosphoric acid, an acidic cation exchanger, sulphuric acid halide, 2-halopyridinium salt, dicyclohexylcarbodi-imide or N,N'-carbonyldiimidazole. One can also allow this reaction to take place in two steps, whereby one first converts the carboxylic acid into a reactive derivative, e.g. an acid chloride, an acid azide or imidazolide, and then brings to reaction with the 4-aminopyridine.

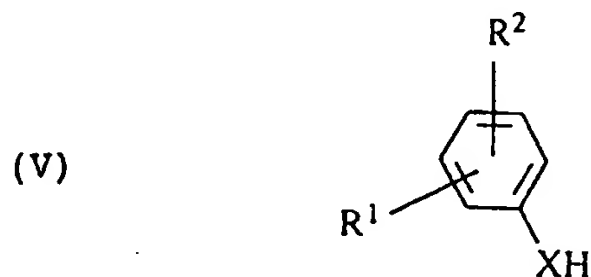
One prepares the carboxylic acids of the general formula III from the esters of the general formula IV



in which  $R^{10}$  signifies an alkyl or benzyl group. Depending upon the nature of this group, the reaction takes place either with the help of bases or acids or hydrogenolytically. If  $R^{10}$  is a methyl or ethyl group, then the reaction preferably takes place with caustic soda solution, caustic potash solution in methanol, ethanol or in water. If  $R^{10}$  is a tert.-butyl group, then the reaction takes place with an acid, preferably hydrochloric acid, formic acid or trifluoroacetic acid. If  $R^{10}$  is a benzyl group, then the reaction preferably takes place hydrogenolytically in the presence of a catalyst, such as palladium on carbon, or with platinum.

From compounds of the general formula IV, in which  $R^1$  signifies the group  $R^6-NH-SO-$ ,  $R^6-NH-SO_2-$ ,  $R^6-SO-NH-$  or  $R^6-SO_2-NH-$ , one can prepare by alkylation another compound of the general formula IV in which  $R^1$  signifies the group  $R^6-NR^{7'}-SO-$ ,  $R^6-NR^{7'}-SO_2-$ ,  $R^6-SO-NR^{7'}$  or  $R^6-SO_2-NR^{7'}$ . As alkylation agents, one uses compounds of the general formula  $R^{7'}-Z$ , whereby  $R^{7'}$  has the same meaning as  $R^7$  with the exception of the hydrogen atom, the phenyl and heteroaryl group and  $Z$  signifies a reactive group, such as halogen, preferably bromine, chlorine, or a sulphate. These reactions are preferably carried out in a solvent, such as acetone, ether, toluene or dimethylformamide, at temperature between  $-30^\circ C$  and  $100^\circ C$ , preferably at room temperatures, in the presence of a base, such as sodium hydride or calcium carbonate.

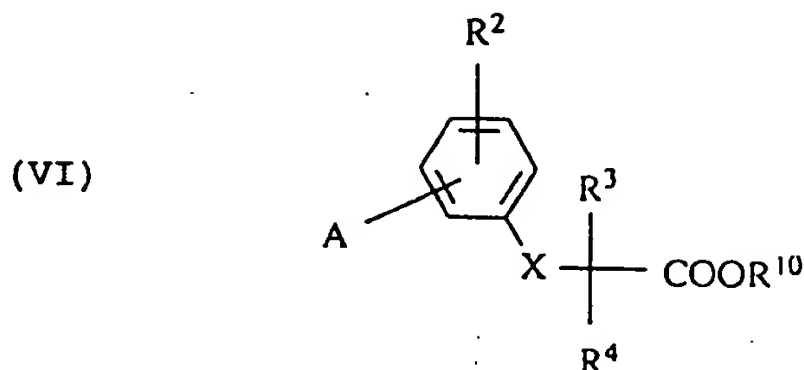
One prepares the compounds of the general formula IV from the compounds of the general formula V



which one reacts with  $\alpha$ -haloesters of the general formula  $Hal-CR^3R^4-CO_2R^{10}$ . By  $Hal$  is to be understood a halogen atom, preferably chlorine and bromine. These reactions are preferably carried out in a solvent, such as acetone, ether, toluene or dimethylformamide, at temperatures between  $-30^\circ C$  and  $100^\circ C$ , preferably at room temperature, in the presence of a base, such as sodium hydride or calcium carbonate.

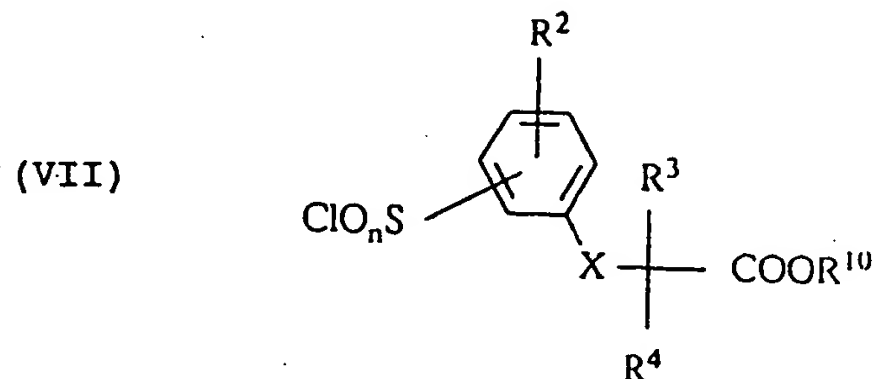
One prepares the compounds of the general formula IV, in which  $R^1$  signifies the group  $R^6-SO-O-$ ,  $R^6-SO_2-O-$ ,  $R^6-$

SO-NH- or  $R^6$ -SO<sub>2</sub>-NH-, from the compounds of the general formula VI



in that one reacts them with a sulphonyl chloride  $R^6$ -SOCl or sulphonyl chloride  $R^6$ -SO<sub>2</sub>Cl.  $A$  thereby signifies a hydroxyl or amino group  $NHR^7$ . The reaction expediently takes place with addition of an acid-binding agent, such as e.g. alkali metal acetate, alkali metal hydroxide, calcium oxide, calcium carbonate, magnesium carbonate or with organic bases, such as pyridine, triethylamine, N-methylmorpholine or diisopropylmethylaniline, whereby as inert solvent, there serve e.g. ether, methylene chloride, dioxane, toluene or an excess of the tertiary amine. In the case of the use of inorganic acid binders, as reaction medium one uses e.g. water, aqueous ethanol or aqueous dioxane.

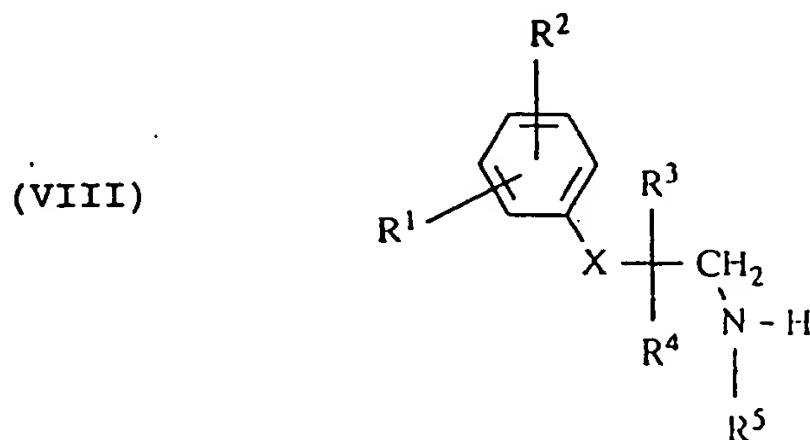
One can prepare the compounds of the general formula IV, in which  $R^1$  signifies the group  $R^6$ -O-SO-,  $R^6$ -O-SO<sub>2</sub>-,  $R^6$ -NR<sup>7</sup>-SO- or  $R^6$ -NR<sup>7</sup>-SO<sub>2</sub>-, from the compounds of the general formula VII,



in which  $n$  is equal to one (sulphinyl chloride) or equal to 2 (sulphonyl chloride). One reacts with compounds of the general formula  $R^6-OH$  or  $R^6-NH-R^7$ , respectively. The reaction expediently takes place with the addition of an acid-binding agent, such as e.g. alkali metal acetate, alkali metal hydroxide, calcium oxide, calcium carbonate, magnesium carbonate or with organic bases, such as pyridine, triethylamine, *N*-methyldimorpholine or diisopropylmethylaniline, whereby, as inert solvent, there serve e.g. ether, methylene chloride, dioxane, toluene or an excess of the tertiary amine. In the case of the use of inorganic acid binders, as reaction medium one uses e.g. water, aqueous ethanol or aqueous dioxane.

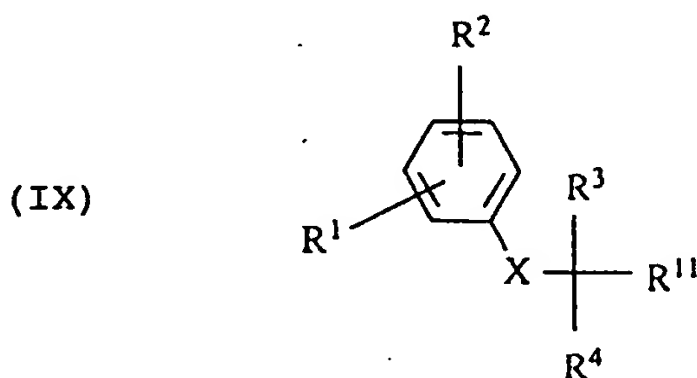
The compounds of the general formulae V and VII are known from the literature (Methoden der Organischen Chemie (Houben-Weyl), Thieme Verlag, Stuttgart 1955: p. 285: M. Quaedvlieg, Aliphatische Sulfinsäuren; p. 299: F. Muth, Aromatische Sulfinsäuren; p. 343: M. Quaedvlieg, Aliphatische Sulfonsäure; p. 429: F. Muth, Aromatische Sulfonsäure: p. 599: F. Muth, Funktionelle *N*-Derivate der Arylsulphonsäure; p. 659: F. Muth, Aromatische Sulfonsäureester) or can be prepared according to the there-described methods. The compounds of the general formula VI are known from the literature (Sobotka, Austin, J. Am. Chem. Soc. 74, 3813 (1952)) or can be prepared by the there-described methods.

A further method for the preparation of compounds of the general formula I consists in the reaction of compounds of the general formula VIII



with a pyridine derivative which has a nucleofugic group which can be removed in position 4. As such groups which can be removed, there come into question halogens, preferably bromine, chloride and fluorine, as well as nitro, alkoxy and phenoxy groups. For the simplification of the reaction, the 4-aminopyridine derivative can contain further halogen atoms, preferably chlorine. Preferred derivatives are pentachloropyridine and 4-nitrotetrachloropyridine. One preferably carries out this reaction in an inert solvent, such as e.g. toluene, dioxane, dimethylformamide, dimethylacetamide, methylene chloride or ethanol, at temperatures between room temperature and the boiling temperature of the solvent, preferably between 20 and 40°C. If the pyridine derivative contains further chlorine atoms, then the nucleophilic reaction is followed by a dehalogenation reaction, e.g. by catalytic hydrogenation.

One prepares the compounds of the general formula VIII by reduction of the compounds of the general formula IX

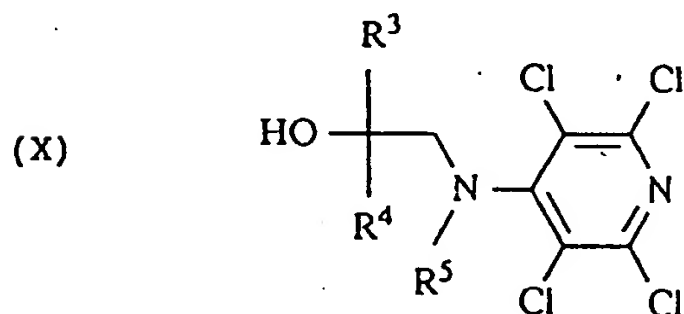


in which R<sup>11</sup> signifies a nitrile group or an amide group CONHR<sup>5</sup>. As reducing agents, there come into consideration complex boron and aluminium hydrides, boron

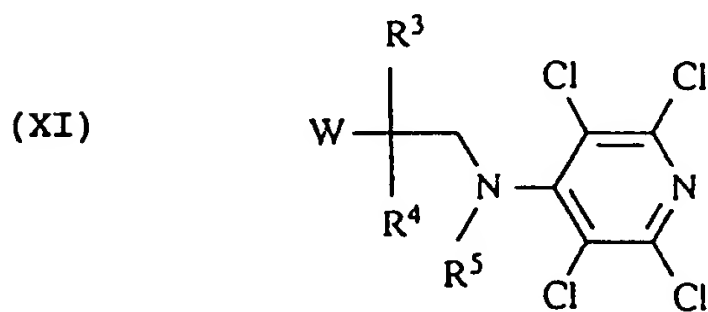
hydride complexes, aluminium hydride, which one prepares in situ by reaction of  $\text{LiAlH}_4$  with  $\text{AlCl}_3$  or sulphuric acid, or a mixture of  $\text{AlCl}_3$  and  $\text{NaBH}_4$ .

One prepares the compounds of the general formula IX from the compounds of the general formula III. The reaction takes place by reaction of equimolar amounts of an amine  $\text{H}_2\text{NR}^5$  and of the carboxylic acid of the general formula III in the presence of a water-removing agent, such as polyphosphoric acid, an acidic cation exchanger, sulphuric acid halide, 2-halopyridinium salt, dicyclohexylcarbodiimide or N,N'-carbonyldiimidazole. One can also allow this reaction to run in two steps, whereby one first converts the carboxylic acid into a reactive derivative, e.g. an acid chloride or an acid azide, and then brings to reaction with ammonia.

A further process for the preparation of compounds of the general formula I starts from the compounds of the general formula X

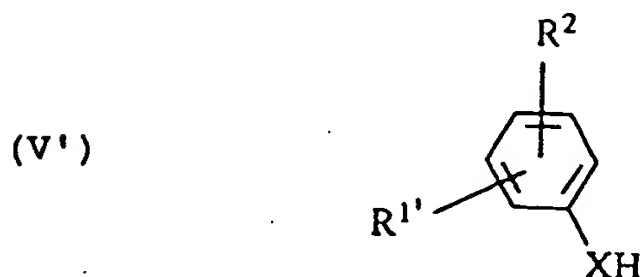


which are obtained according to methods known from the literature (M.M. Boudakian, in Heterocyclic Compounds, Vol. 14, Suppl. Part. 2, (R.A. Abramovitch, Ed.), Wiley, New York 1974, page 407) by reacting the commercially available aminoethanols  $\text{HO-CR}^3\text{R}^4\text{-CH}_2\text{-NHR}^5$  with pentachloropyridine or 4-nitrotetrachloropyridine in an inert solvent such as dioxane, tetrahydrofuran, methylene chloride or ethanol at temperatures between  $-10^\circ\text{C}$  and the boiling temperature of the solvent. The hydroxy group of compounds of the general formula X is converted into a leaving group W and by this means compounds of the general formula XI are obtained



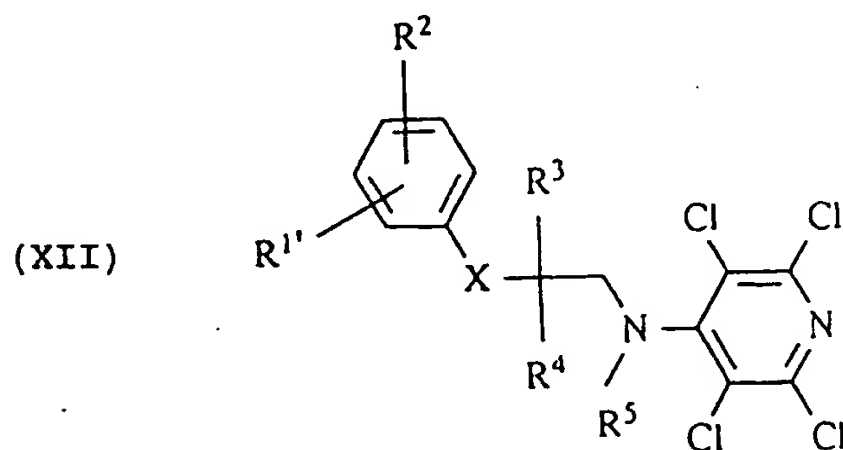
in which W denotes a halogen atom such as chlorine or bromine or a sulfonic acid ester such as tosyloxy. The conversion of the hydroxy group into a halogen atom is carried out with a halogenation agent such as thionyl chloride or phosphoryl chloride, conversion into a sulfonic acid ester is carried out by reaction with a sulfonyl chloride such as tosyl chloride.

The compounds of the general formula XI are then reacted with compounds of the general formula V'

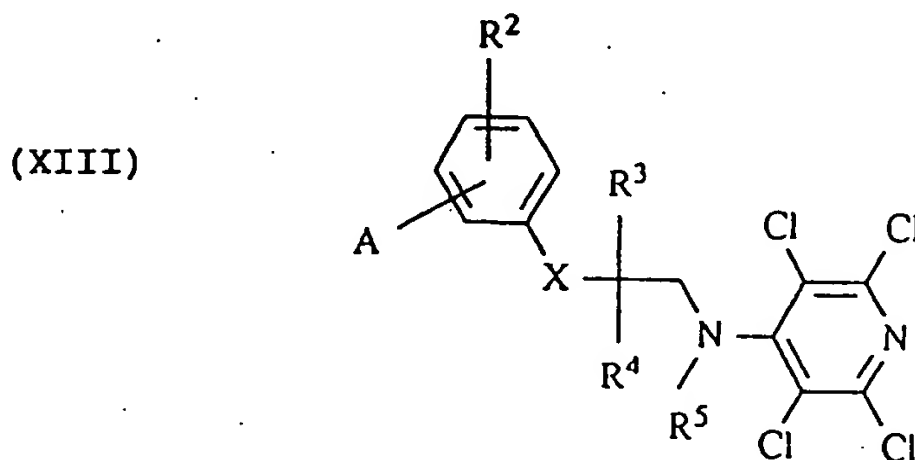


in which  $R^{1'}$  has the same meaning as  $R^1$  but additionally can also be a protected hydroxyl group or amino group. By a protected hydroxyl group, one understands the benzyloxy group or the acetyloxy group. By the protected

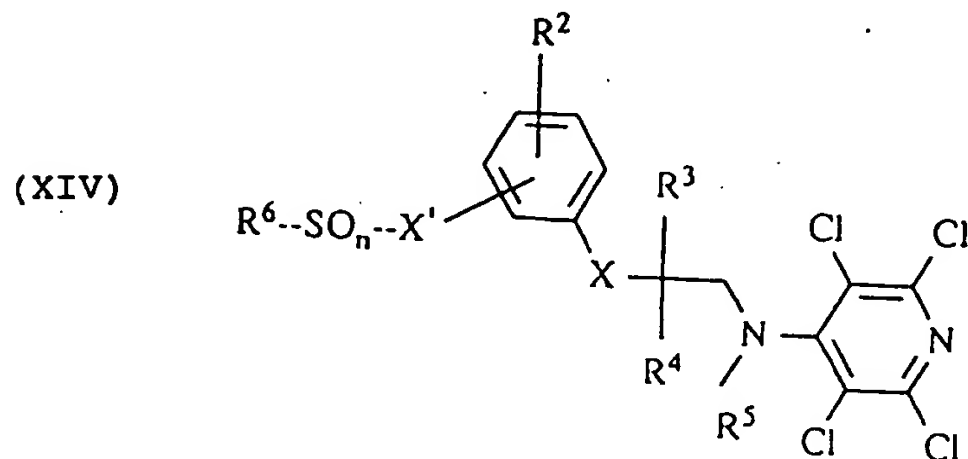
amino group one preferably understands the tert.-butyl-oxy-carbamoyl group, the benzyloxycarbamoyl group, the dibenzylamino group or the phthalimido group. The compounds of the general formula XII thereby result. The reaction of compounds of the general formula V' with compounds of the general formula X instead of XI according to Mitsunobu in the presence of triphenylphosphine and diazodicarboxylic acid diethyl ester or piperidide also leads to compounds of the general formula XII,



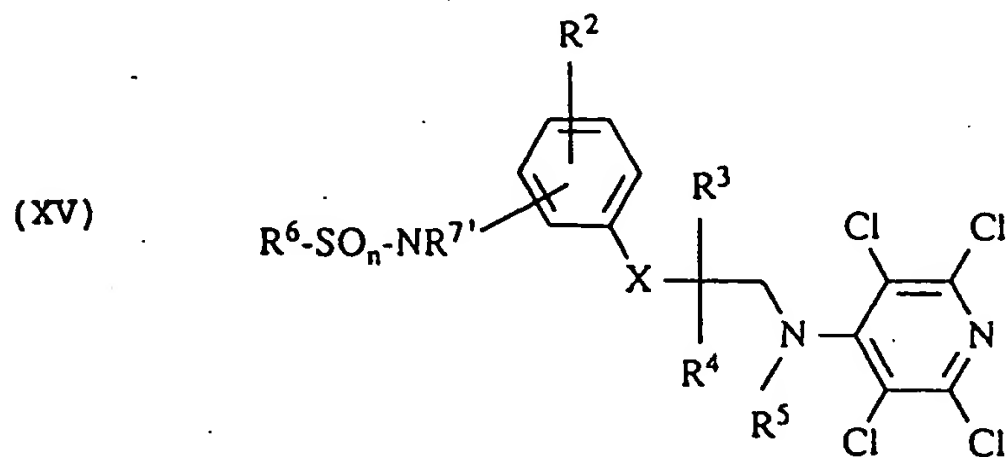
If  $R^{1'}$  in the compounds of the general formula XII is a protected hydroxyl group or a protected amino group, then now, in the next step, the protective group is removed. This takes place for the benzyl protective group by hydrogenolysis in the presence of a catalyst, such as palladium on carbon, for the tert.-butylcarbamoyl group by a strong acid, such as trifluoroacetic acid, and for the acetyl group by a base, such as caustic soda solution. Compounds of the general formula XIII thereby result,



which, by reaction with sulphonyl chloride or sulphonyl chloride, one converts into compounds of the general formula XIV,



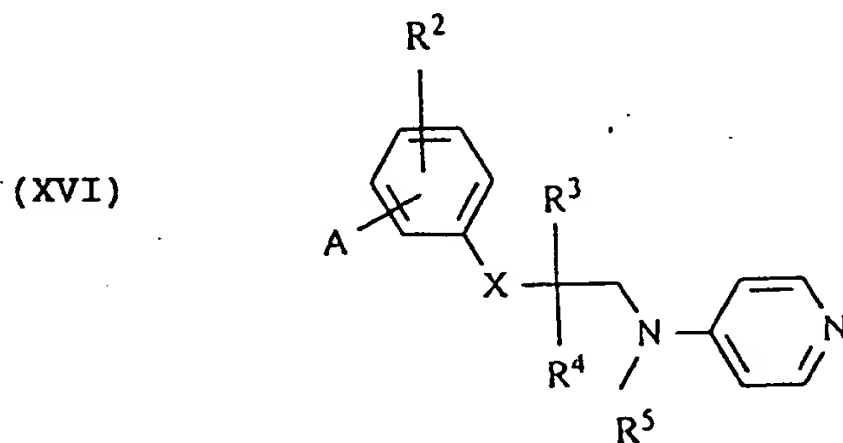
in which  $n = 1$  or  $2$  and  $X'$  signifies the oxygen atom or the imino group  $NH$ . If  $X'$  signifies an imino group, then compounds of the general formula XIV are now converted into the compounds of the general formula XV



in which  $R^{7'}$  has the same meaning as  $R^7$  with the exception of the hydrogen atom. This takes place by reaction with the alkylation agents  $R^{7'}-Y$  as is described in the case of the alkylations of the general formula IV.

One finally obtains the compounds of the general formula I from the compounds of the general formula XII, in which  $R^1$  has the same meaning as  $R^1$ , from the compounds of the general formula XIV, or from the compounds of the general formula XV by removal of the chlorine atoms of the pyridine ring. This takes place by catalytic hydrogenation in the presence of a catalyst, such as Raney nickel or palladium on carbon, in the presence of a base, such as potassium carbonate, sodium hydrogen carbonate or sodium methylate.

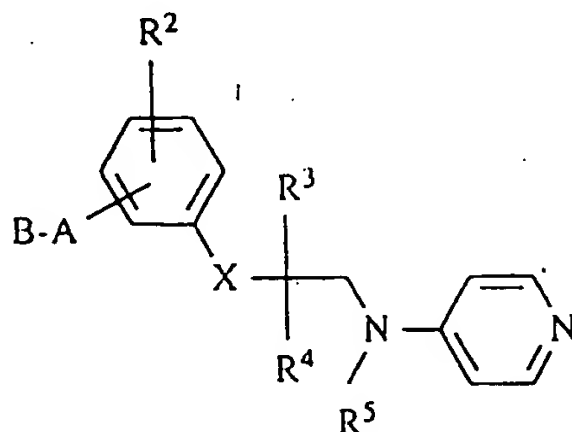
For the preparation of compounds of general formula I, in which  $R^1$  signifies the group  $R^6-SO-NR^7-$ ,  $R^6-SO_2-NR^7-$ ,  $R^6-SO-O-$  or  $R^6-SO_2-O-$ , there exists a further synthesis route in the reaction of compounds of the general formula XVI



with a sulphinyl chloride  $R^6-SOCl$  or a sulphonyl chloride  $R^6-SO_2-Cl$ , respectively. The reaction takes place as described for the reaction with compounds of the general formula VI.  $A$  thereby signifies the hydroxyl group or an amino group  $NHR^7$ .

One prepares compounds of the general formula XVI from the compounds of the general formula XVII

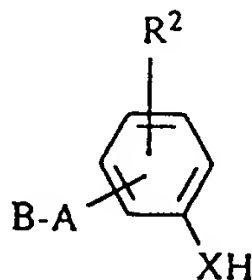
(XVII)



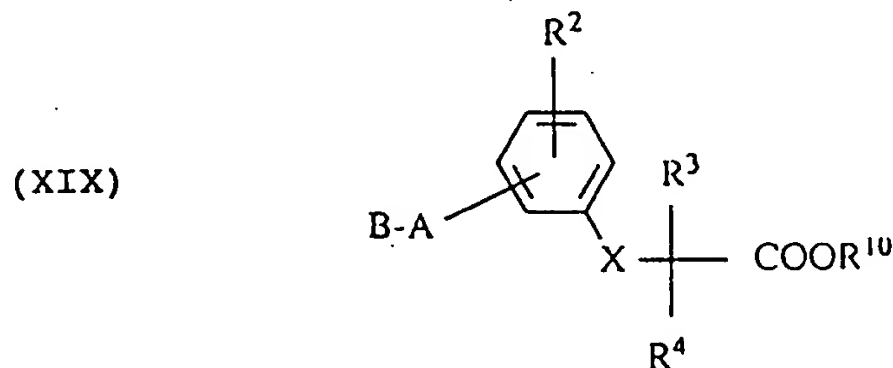
in which B signifies a protective group which is split off for the preparation of compounds of the general formula XVI. As protective groups B, there come into question the benzyl group, which one removes hydrolytically in the presence of a catalyst, such as palladium on charcoal, the tert.-butyloxycarbonyl group, which one removes by the action of acids, such as trifluoroacetic acid, formic acid or hydrochloric acid, or an aromatic sulphonyl group, such as the benzene-sulphonyl or tosyl group, which one removes by the action of alkali, such as caustic soda solution or caustic potash solution.

One prepares compounds of the general formula XVII according to the same principles as compounds of the general formula I. Preferably one starts from compounds of the general formula XVIII

(XVIII)



which one reacts with haloesters of the general formula  $\text{Hal-CR}^3\text{R}^4\text{-CO}_2\text{R}^{10}$  as is described for the reactions with compounds of the general formula V. Compounds of the general formula XIX thereby result



which, after saponification of the ester and activation of the acid function, one reacts, as described in the case of the compounds of the general formula III, with 4-aminopyridine or  $\text{N-R}^5$ -4-aminopyridine to give compounds of the general formula XVI.

Certain compounds of the general formula I can subsequently be converted into other compounds of the general formula I.

This concerns compounds of the general formula I, in which the groups  $\text{R}^5$ ,  $\text{R}^6$  or  $\text{R}^7$  signify the benzyl group, or in which  $\text{R}^6$  signifies an aryl or heteroaryl group which, as substituents, carry one or more benzyloxy, benzylamino or benzyloxycarbonyl groups. By catalytic hydrogenation in the presence of a catalyst, preferably palladium on carbon, the benzyl group is thereby replaced.

by the hydrogen atom. The removal of the benzyl group also takes place by reaction with a strong acid, such as trifluoroacetic acid, in the presence of mesitylene, anisole or thioanisole.

This also concerns compounds of the general formula I, in which  $R^6$  signifies an aryl or heteroaryl group, which as substituents, carry one or more chlorine atoms. By catalytic hydrogenation in the presence of a catalyst, preferably palladium on carbon, the chlorine atom is thereby replaced by the hydrogen atom.

This also concerns compounds of the general formula I, in which  $R^6$  signifies an aryl or heteroaryl group, which, as substituents, carry one or more nitro groups. By catalytic hydrogenation in the presence of a catalyst, preferably palladium on carbon.

This also applies to compounds of the general formula I in which  $R^6$  denotes an aryl or heteroaryl group which carry an alkyloxycarbonyl, alkyloxycarbonylalkyl or alkyloxycarbonylalkyloxy group as substituents or the group  $R^7$  denotes an alkoxycarbonylalkyl group. In this case the free carboxylic acids can be produced from the alkoxycarbonyl groups by reaction with acids such as hydrochloric acid, or bases such as sodium hydroxide. If these alkoxycarbonyl groups are reacted with an amine of the general formula  $NHR^8R^9$ , then a  $CONR^8R^9$  group is formed from the alkoxycarbonyl group. If these alkoxycarbonyl groups are treated with a reducing agent such as  $LiAlH_4$  then the corresponding hydroxymethyl groups are formed from this.

This also applies to compounds of the general formula I in which  $R^6$  denotes an aryl or heteroaryl group which carry one or several nitriles, cyanoalkyl, cyanoalkoxy, formylamino, alkylcarbonylamino, aminocarbonyl, alkylaminocarbonyl groups or a  $-S-Y-CONHR^8$ ,  $-O-Y-CONHR^8$ ,  $-NH-Y-CONHR^8$  group as substituents or in which  $R^7$  denotes a cyanoalkyl, aminocarbonylalkyl or the group  $-Y-CONHR^8$ . These groups can be reduced preferably with  $LiAlH_4$  to form the corresponding aminomethyl compounds.

Examples of salts of compounds of formula I which can be used physiologically are salts with physiologically tolerated mineral acids such as hydrochloric acid, sulphuric acid, sulphurous acid or phosphoric acid; or with organic acids such as methanesulfonic acid, p-toluenesulfonic acid, acetic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. The compounds of formula I with a free carboxy group can also form salts with physiologically tolerated bases. Examples of such salts are alkaline metal, alkaline-earth metal, ammonium and alkylammonium salts such as a sodium, potassium, calcium or tetramethylammonium salt.

The compounds of formula I can be solvated and in particular hydrated. The hydration can be achieved in the course of the production process or gradually occur as a result of hygroscopic properties of a compound of formula I which is firstly anhydrous.

Pure enantiomers of compounds of formula I can either be obtained by racemate resolution (by formation of salts

with optically active bases) or by using optically active starting materials in the synthesis.

For the production of pharmaceutical agents, the substances of the general formula I are mixed with suitable pharmaceutical carrier substances, aromatics, flavourings and dyes and are for example formed into tablets or coated tablets or are suspended or dissolved in water or oil e.g. olive oil with the addition of appropriate auxiliary substances.

The substances of the general formula I and their salts can be administered enterally or parenterally in a liquid or solid form. Water is preferably used as an injection medium which contains the usual additives in injection solutions such as stabilizers, solubilizers or buffers. Such additives are e.g. tartrate and citrate buffer, complexing agents (such as ethylenediaminetetraacetic acid and their non-toxic salts) and high molecular polymers such as liquid polyethyloxyde in order to regulate viscosity. Solid carrier materials are for example starch, lactose, mannitol, methylcellulose, talcum, highly dispersed silicic acids, high molecular fatty acids (such as stearic acid), animal and vegetable fats and solid high molecular polymers (such as polyethylene glycols). Preparations suitable for oral administration can, if desired, contain flavourings and sweeteners.

The compounds are usually administered in amounts of 10-1500 mg per day in relation to 75 kg body weight. It is preferable to administer 1-2 tablets with a content of active substance of 5-500 mg, 2-3 times per day. The tablets can also be retarded as a result of which only

1-2 tablets have to be administered per day with 20-700 mg active substance. The active substance can also be administered by injection 1-8 times per day or by continuous infusion in which case 50-2000 mg per day are usually sufficient.

The following compounds are preferred within the sense of the invention in addition to those mentioned in the examples:

1. Benzenesulfinic acid-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester
2. N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfinamide
3. 3-{3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenylaminosulfonyl}-phenoxy-acetic acid
4. 2-{3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenylaminosulfonyl}-phenoxy-acetic acid
5. 3-{3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenylaminosulfonyl}-phenoxy-acetamide
6. N-(2-Hydroxyethyl)-3-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenylaminosulfonyl}-phenoxy-acetamide
7. N-(2,3-Dihydroxypropyl)-3-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenylaminosulfonyl}-phenoxy-acetamide

8. N-(2-Hydroxyethyl)-3-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyloxysulfonyl}-phenoxy-acetamide
9. 3-{3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenylaminosulfonyl}-phenoxy-acetic acid-morpholide
10. Acetic acid 2-[2-(benzenesulfonyl-{3-methyl-5-[2-pyridin-4-ylamino)-ethoxy]-phenyl}-aminoacetyl-amino]-ethyl ester
11. Acetic acid 3-[2-(benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino-acetyl-amino)-propyl ester
12. Acetic acid 2-[2-(2-methoxybenzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino-acetyl-amino)-ethyl ester
13. N-{3-Cyano-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide

**Example 1**N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-2-naphthalene-sulfonamide

- a) 6.3 g (28 mmol) naphthalene-2-sulfonyl chloride in 30 ml methylene chloride was added dropwise at 10°C to 5.9 g (25 mmol) 3-aminophenoxyacetic acid ethyl ester and 6.9 ml triethylamine in 100 ml methylene chloride while cooling on ice. It was stirred for 1 hour at room temperature, extracted with water and the organic phase was dried over sodium sulfate. The solvent was removed in a vacuum and 9.6 g N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-2-naphthalene-sulfonamide was obtained as an oil. MS m/e = 385.
- b) 4.2 g (75 mmol) potassium hydroxide was added to 9.6 g (25 mmol) of this compound in 100 ml ethanol and it was stirred for 1 hour at 70°C. It was filtered, the precipitate was dissolved in water, acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The solvent was removed in a vacuum, the residue was dissolved in 2 N sodium hydroxide solution, acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and the solvent was removed in a vacuum. The oily residue crystallizes on standing. 7.6 g (85 %) N-{3-[(carboxy)-methoxy]-phenyl}-2-naphthalene-sulfonamide was obtained. Fp. 153 - 155°C. FAB-MS: M+H = 358.

- c) 2.7 g (16.8 mmol) 1,1-carbonyldiimidazole was added to 3 g (8.4 mmol) of this compound in 30 ml tetrahydrofuran at 45°C and it was stirred for 20 minutes. 0.8 g (8.4 mmol) 4-aminopyridine was added to this and stirred for 6 hours at 60°C. Then 2.7 g (16.8 mmol) 1,1-carbonyldiimidazole and 0.8 g (8.4 mmol) 4-aminopyridine was again added and it was stirred for a further 6 hours at 60°C. The solvent was removed in a vacuum, the residue was taken up in ethyl acetate and extracted with aqueous sodium bicarbonate and with phosphate buffer, pH = 7.0. The organic phase was dried over sodium sulfate, filtered and the solvent was removed in a vacuum. 2.5 g (69 %) N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-2-naphthalene-sulfonamide was obtained. Fp. 204 - 207°C.

MS m/e = 433.

- d) 2.0 g (4.6 mmol) of this compound was added under nitrogen to 1.0 g (20.4 mmol) lithium aluminium hydride in 20 ml tetrahydrofuran and it was boiled for 1 hour under reflux. Excess  $\text{LiAlH}_4$  was decomposed with water, filtered and the filtrate was concentrated by evaporation in a vacuum. The residue was taken up in ethyl acetate, extracted with water, the organic phase was dried with sodium sulfate, filtered and the solvent was removed in a vacuum. The oily residue was separated on a reverse-phase column (RP-18; mobile solvent: methanol/water pH = 6.8, 7:3). The desired fraction was evaporated to dryness in a vacuum and extracted with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and the solvent was removed in a vacuum. 0.3 g (16 %) of the title

compound was obtained of Fp. 90 - 91°C.

MS m/e = 419.

Example 2

N-{3-[2-[Pyridin-4-ylamino)-ethoxy]-phenyl}-1-naphthalene-sulfonamide

The production was carried out analogously to example 1 except that in step a) 1-naphthalene-sulfonyl chloride was used instead of 2-naphthalenesulfonyl chloride.

Intermediate steps:

- a) N-{3-[(Ethoxycarbonyl)-methoxy]-phenyl}-1-naphthalenesulfonamide as an oil. MS m/e = 385.
- b) N-{3-[(Carboxy)-methoxy]-phenyl}-1-naphthalene-sulfonamide. Fp. 147 - 149°C. FAB-MS: M+H = 358.
- c) N-{3-[(Pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-1-naphthalenesulfonamide. Fp. 210 - 211°C (decomp.). MS m/e = 433.
- d) Title compound. Yield 38 %. Fp. 239 - 241°C (decomp.). MS: pos. LSIMS m/e = 419

**Example 3****4-Methyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide**

The production was carried out analogously to example 1 except that in step a) 4-toluenesulfonyl chloride was used instead of 2-naphthalenesulfonyl chloride.

**Intermediate steps:**

- a) 4-Methyl-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulfonamide. Fp. 100 - 102°C. MS m/e = 349.
- b) 4-Methyl-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulfonamide. Fp. 170 - 173°C. FAB-MS: M+H = 322.
- c) 4-Methyl-N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulfonamide as an oil. MS m/e = 397.
- d) Title compound. Yield 26 %. Fp. 165 - 167°C. MS m/e = 383.

**Example 4****4-Fluoro-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide-hydrochloride**

The production was carried out analogously to example 1 except that in step a) 4-fluoro-

benzenesulfonyl chloride was used instead of 2-naphthalenesulfonyl chloride.

Intermediate steps:

- a) 4-Fluoro-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulfonamide Fp. 94 - 96°C. MS m/e = 353.
- b) 4-Fluoro-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulfonamide. Fp. 154 - 156°C. FAB-MS: M+H = 326.
- c) 4-Fluoro-N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulfonamide. MS m/e = 401.
- d) Title compound. The base was ground with hydrochloric acid in ether: Yield 21 %. Fp. 203 - 205°C. MS m/e = 387.

Example 5

4-Chloro-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide hydrochloride

The production was carried out analogously to example 1 except that in step a) 4-chloro-benzenesulfonyl chloride was used instead of 2-naphthalenesulfonyl chloride.

Intermediate steps:

- a) 4-Chloro-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulfonamide. MS m/e = 369.
- b) 4-Chloro-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulfonamide. Fp. 190 - 192°C. FAB-MS: M+H = 342.
- c) 4-Chloro-N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulfonamide. Fp. 168 - 171°C. MS m/e = 417.
- d) 1.79 ml (3.58 mmol) 2 M borane dimethylsulfide in tetrahydrofuran was added to 0.65 g (1.55 mmol) from step c) in 15 ml dry tetrahydrofuran. It was stirred for 3 hours at 60°C and 10 ml methanol was then added in an ice bath. 5 ml hydrogen chloride in ether was added. The solvent was removed in a vacuum and the residue was ground with warm water. 0.13 g of the title compound was obtained of Fp. 241 - 243°C. MS m/e = 403.

#### Example 6

#### 4-Trifluoromethyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide

It was produced analogously to example 1 except that in step a) 4-trifluoromethyl-benzenesulfonyl chloride was used instead of 2-naphthalenesulfonyl chloride.

Intermediate steps:

- a) 4-Trifluoromethyl-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulfonamide. MS m/e = 403.
- b) 4-Trifluoromethyl-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulfonamide. Fp. 155 - 158°C. FAB-MS: M+H = 375.
- c) 4-Trifluoromethyl-N-{3-[(pyridin-4-ylamino-carbonyl)-methoxy]-phenyl}-benzenesulfonamide. Fp. 66 - 68°C. MS m/e = 451.
- d) Title compound Fp. 145 - 148°C. MS m/e = 437.

**Example 7**

**3-Trifluoromethyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide**

It was produced analogously to example 1 except that 3-trifluoromethyl-benzenesulfonyl chloride was used instead of 2-naphthalenesulfonyl chloride.

**Intermediate steps:**

- a) 3-Trifluoromethyl-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulfonamide. MS m/e = 403.
- b) 3-Trifluoromethyl-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulfonamide. Fp. 147 - 149°C. FAB-MS: M+H = 375.

- c) 3-Trifluoromethyl-N-{3-[(pyridin-4-ylamino-carbonyl)-methoxy]-phenyl}-benzenesulfonamide as an oil. MS m/e = 451.
- d) Title compound. Fp. 185 - 187°C. MS m/e = 437.

Example 8

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-cyclohexane-sulfonamide

It was produced analogously to example 1 except that in step a) cyclohexyl-sulfonyl chloride was used instead of 2-naphthalenesulfonyl chloride.

Intermediate steps:

- a) N-{3-[(Ethoxycarbonyl)-methoxy]-phenyl}-cyclohexanesulfonamide. MS m/e = 341.
- b) N-{3-[(Carboxy)-methoxy]-phenyl}-cyclohexane-sulfonamide. Fp. 132°C. FAB-MS: M+H = 313.
- c) N-{3-[(Pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-cyclohexanesulfonamide as an oil. MS m/e = 389.
- d) Title compound. MS m/e = 375.

**Example 9****N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide**

It was produced analogously to example 1 except that in step a) benzenesulfonyl chloride was used instead of 2-naphthalenesulfonyl chloride.

**Intermediate steps:**

- a) N-{3-[(Ethoxycarbonyl)-methoxy]-phenyl}-benzenesulfonamide as an oil. MS m/e = 335.
- b) N-{3-[(Carboxy)-methoxy]-phenyl}-benzenesulfonamide. Fp. 160 - 161°C. FAB-MS: M+H = 307
- c) N-{3-[(Pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulfonamide. Fp. 151 - 156°C. MS m/e = 383.
- d) Title compound. Yield 26 %. Fp. 182 - 184°C. MS m/e = 369.

**Example 10****N-{3-[1-Methyl-2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide**

- a) 5.6 ml (44 mmol) benzenesulfonyl chloride was added dropwise at 10°C to 8.4 g (40 mmol) 2-(3-amino-phenoxy)-propionic acid ethyl ester and 6.1 ml (44 mmol) triethylamine in 50 ml methylene chloride

while cooling on ice. It was stirred for 1 hour at room temperature, extracted with water, the organic phase was dried with sodium sulfate, filtered and the solvent was removed in a vacuum. 14 g N-{3-[1-(ethoxycarbonyl)-ethoxy]-phenyl}-benzenesulfonamide was obtained as an oil. MS m/e = 349.

- b) 14 g (40 mmol) of this compound and 6.7 g (120 mmol) potassium hydroxide in 100 ml ethanol were stirred for 1 hour at 70°C. It was extracted twice with ethyl acetate, acidified with half-concentrated hydrochloric acid and again extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and the solvent was removed in a vacuum. 9.2 g (72 %) N-{3-[1-(carboxy)-ethoxy]-phenyl}-benzenesulfonamide was obtained as an oil. MS m/e = 321.
- c) 3.4 g (57 %) N-{3-[1-(pyridin-4-ylaminocarbonyl)-ethoxy]-phenyl}-benzenesulfonamide (Fp. 142 - 144°C. MS m/e = 397) was produced as in example 1, step c) from 4.8 g (15 mmol) of this compound, 2.1 g (22.5 mmol) 4-aminopyridine and 3.2 g (19.5 mmol) 1,1-carbonyl-diimidazole in 40 ml tetrahydrofuran.
- d) 0.6 g (37 %) of the title compound (Fp. 162 - 163°C. MS m/e = 383) was produced from 1.7 g (4.3 mmol) of this compound and 0.65 g (17.2 mmol) lithium aluminium hydride in 20 ml tetrahydrofuran as in example 1, step d).

Example 11N-{3-[1,1-Dimethyl-2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide

The compound was produced analogously to example 10. 2-methyl-2-(3-aminophenoxy)-propionic acid ethyl ester was used in step a) instead of 2-(3-aminophenoxy)-propionic acid ethyl ester.

- a) N-{3-[1-Methyl-1-(ethoxycarbonyl)-ethoxy]-phenyl}-benzenesulfonamide as an oil. MS m/e = 363.
- b) N-{3-[1-Methyl-(carboxy)-ethoxy]-phenyl}-benzenesulfonamide as an oil. MS m/e = 335.
- c) N-{3-[1-Methyl-(pyridin-4-ylaminocarbonyl)-ethoxy]-phenyl}-benzenesulfonamide. Fp. 141 - 143°C.  
MS m/e = 411.
- d) Title compound as an oil. MS m/e = 397.

Example 12N-Methyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide hydrochloride

- a) A solution of 1.6 ml (25 mmol) iodomethane in 10 ml dimethylformamide was added dropwise at 80 - 90°C to 8.4 g (25 mmol) N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulfonamide (example 9, step a) and 3.5 g potassium carbonate in 10 ml dimethyl-

formamide. It was stirred for a further 2 h at this temperature, allowed to cool to room temperature, filtered and the filtrate was concentrated in a vacuum. The residue was taken up in ethyl acetate and extracted with water. It was dried over sodium sulfate, filtered and the solvent was removed in a vacuum. 8.6 g N-methyl-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulfonamide was obtained as an oil. MS m/e = 349.

- b) The further reaction was carried out as in example 1; step b. N-methyl-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulfonamide was obtained. Fp.: 110 - 111°C. MS m/e = 321.
- c) N-Methyl-N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulfonamide. Fp.: 76 - 78°C. MS m/e = 397.
- d) Title compound. 2 N hydrochloric acid was added to the free base, it was extracted with ethyl acetate and the aqueous phase was evaporated to dryness. An oil was obtained which crystallized after grinding with isopropanol. Yield 46 %. Fp.: 174 - 176°C.

### Example 13

#### N-Ethyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide

It was produced analogously to example 12 except that iodoethane was used instead of iodomethane in step a).

2156729

- 45 -

- a) N-Ethyl-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulfonamide as an oil. MS m/e = 363.
- b) N-Ethyl-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulfonamide. Fp.: 122°C. MS m/e = 335.
- c) N-Ethyl-N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulfonamide. MS m/e = 411.
- d) Title compound as an oil. MS m/e = 397.

Example 14

N-Propyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide

It was produced analogously to example 12 except that iodopropane was used instead of iodomethane in step a).

- a) N-Propyl-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulfonamide as an oil. MS m/e = 377.
- b) N-Propyl-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulfonamide. Fp.: 147°C. MS m/e = 349.
- c) N-Propyl-N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulfonamide. Fp. 105°C. MS m/e = 425.
- d) Title compound as an oil. MS m/e = 411.

**Example 15****N-Benzyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide**

It was produced analogously to example 12 except that benzyl bromide was used instead of iodomethane in step a).

- a) N-Benzyl-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulfonamide as an oil. MS m/e = 425.
- b) N-Benzyl-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulfonamide. Fp.: 190°C. MS m/e = 397.
- c) N-Benzyl-N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulfonamide. Fp. 140°C. MS m/e = 473.
- d) Title compound. Fp.: 128°C. MS m/e = 459.

**Example 16****N-Allyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide**

It was produced analogously to example 12 except that allyl bromide was used instead of iodomethane in step a).

- a) N-Allyl-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulfonamide as an oil. MS m/e = 375.

2156729

- 47 -

- b) N-Allyl-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulfonamide. MS m/e = 347.
- c) N-Allyl-N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulfonamide. MS m/e = 423.
- d) Title compound as an oil. MS m/e = 409.

Example 17

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide hydrochloride

It was produced analogously to example 12 except that in step a) benzenesulfonyl chloride was used instead of 2-naphthalenesulfonyl chloride and 3-amino-5-methyl-phenoxyacetic acid ethyl ester instead of 3-amino-phenoxyacetic acid ethyl ester.

Intermediate steps:

- a) N-{5-Methyl-3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulfonamide as an oil. MS m/e = 349.
- b) N-{5-Methyl-3-[(carboxy)-methoxy]-phenyl}-benzenesulfonamide. Fp.: 156 - 159°C. FAB-MS: M+H = 322.
- c) N-{5-Methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulfonamide. Fp.: 193 - 196°C. MS m/e = 397.

- d) Title compound. Yield 56 %. Fp. 170°C.  
MS m/e = 383.

**Example 18**

Benzenesulfonic acid-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

- a) 0.44 g (0.011 mol) sodium hydride (60 % in white oil) is added to 2.5 g (0.01 mol) benzenesulfonic acid-3-hydroxyphenyl ester in 30 ml acetonitrile while cooling at 10°C and it is stirred for 1 hour at this temperature. 2.2 ml (0.02 mol) ethyl bromoacetate in 10 ml acetonitrile is added dropwise within 30 minutes and it is stirred for 3 hours at room temperature. After addition of 5 ml isopropanol, the solvent is removed in a vacuum. 30 ml ethanol, 50 ml water and 0.8 g (0.015 mol) potassium hydroxide are added to the residue. After 16 hours at room temperature, the ethanol is removed in a vacuum and the aqueous solution is extracted three times with ether. The aqueous phase is acidified with hydrochloric acid and extracted with ether. The ether is removed in a vacuum and 1.5 g (48 %) 2-[3-(phenylsulfonyloxy)-phenyloxy]-acetic acid with a Fp. of 152 - 155°C is obtained.
- b) 1.4 g (4.5 mmol) of this compound and 958 mg (5.9 mmol) carbonyldiimidazole are stirred for 30 minutes at 45°C. 0.64 g (6.8 mmol) 4-amino-pyridine is added and it is stirred for two days at 60°C. The solvent is removed in a vacuum and the residue is dissolved in ethyl acetate which contained 0.5 % acetic acid. The organic phase is

dried, filtered and the solvent is removed in a vacuum. The residue is ground with ether, filtered and 1.8 g (94 %) N-(4-pyridinyl)-2-[3-(phenylsulfonyloxy)-phenyloxy]-acetamide of Fp. 127 - 130°C is obtained.

- c) 2.23 ml (18 mmol) chlorotrimethylsilane is added at 5°C to 192 mg (8.8 mmol) lithium borohydride in 5 ml dry tetrahydrofuran while cooling in an ice bath. After 30 minutes 1.7 g (4.4 mmol) of the compound from step b) is slowly added at 5°C. After 16 hours at room temperature it is decomposed with 3 ml methanol and the solvent is removed in a vacuum. The residue is taken up in ethyl acetate and bicarbonate solution. The ethyl acetate phase is purified on a silica gel column (ethyl acetate /methanol = 9:1). The solvent is removed in a vacuum and 1.3 g of the title compound (80 %) is obtained as a viscous oil. FAB-MS: M+H 371.

Example 19

N-Methyl-N-phenyl-3-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulfonamide

- a) 3-Nitrobenzenesulfonic acid-N-methyl-anilide  
5 g 3-nitrobenzenesulfonic acid-chloride is dissolved in 20 ml absolute pyridine and 2.7 ml N-methylaniline is added while cooling on ice and stirring. It is stirred for a further 2 hours at room temperature, the reaction mixture is poured onto ice water and acidified with dilute hydrochloric acid. The aqueous phase is extracted with ethyl acetate, the ethyl acetate phase is

dried over sodium sulfate and evaporated. The residue is recrystallized from alcohol. Yield: 6.3 g. Fp. 90°C.

b) 3-Aminobenzenesulfonic acid-N-methyl-anilide

6 g 3-nitrobenzenesulfonic acid-N-methylanilide is dissolved in 100 ml absolute tetrahydrofuran and hydrogenated after addition of 0.5 g Pd/C (10 %) catalyst. After the calculated amount of hydrogen has been taken up, it is filtered from the catalyst and the filtrate is concentrated by evaporation. Yield: 5.5 g. Fp. 104°C.

c) 3-Hydroxybenzenesulfonic acid-N-methyl-anilide

5 g 3-aminobenzenesulfonic acid-N-methylanilide is dissolved in 20 ml 50 % sulphuric acid. A solution of 1.75 g sodium nitrite in 5 ml water is added dropwise to this while cooling on ice and stirring. When the diazotization is completed, the reaction mixture is heated for 20 minutes to 100°C, it is allowed to cool and extracted with ethyl acetate. The ethyl acetate phase is dried over sodium sulfate and evaporated. The residue is sufficiently pure for further processing.

d) [3-(Methyl-phenyl-sulfamoyl)-phenoxy]-acetic acid ethyl ester

3.5 g 3-hydroxybenzenesulfonic acid-N-methylanilide is dissolved in 20 ml absolute dimethylformamide. 2 g potassium carbonate and 1.9 ml ethyl bromoacetate are added to this and the mixture is heated for 3 hours to 100°C. It is cooled and the solvent is removed by distillation in a vacuum. The

residue obtained (4.3 g) is sufficiently pure for further processing.

- e) [3-[Methyl-phenyl-sulfamoyl]-phenoxy]-acetic acid  
4.2 g [3-[methyl-phenyl-sulfamoyl]-phenoxy]-acetic acid ethyl ester is dissolved in 40 ml ethanol. 1 g potassium hydroxide is added to this and the mixture is stirred for one hour at 90°C. It is cooled to room temperature, acidified with dilute hydrochloric acid and extracted with methylene chloride. The methylene chloride phase is dried over sodium sulfate and evaporated. 4 g [3-[methyl-phenyl-sulfamoyl]-phenoxy]-acetic acid is obtained as an amorphous solid.
- f) 2-[3-(Methyl-phenyl-sulfamoyl)-phenoxy]-N-pyridin-4-yl-acetamide  
2 g [3-(methyl-phenyl-sulfamoyl)-phenoxy]-acetic acid is dissolved in 20 ml absolute tetrahydrofuran. 1.35 g carbonyldiimidazole is added to this and the mixture is heated for 20 minutes to 45°C. It is cooled to room temperature, 900 mg 4-aminopyridine is added and it is stirred for a further 3 hours at 60°C. The solvent is removed by distillation, the residue is dissolved in ethyl acetate and extracted by shaking with water. The ethyl acetate phase is dried over sodium sulfate and evaporated. The residue is chromatographed on a silica gel column for purification (eluting agent: methylene chloride/ methanol 9:5). After evaporating the column fractions, 1.5 g of the title compound is obtained as an amorphous solid.  
FAB-MS: M+H 398.

g) N-Methyl-N-phenyl-3-[2-(pyridin-4-ylamino-ethoxy)-benzenesulfonamide

800 mg 2-[3-(methyl-phenyl-sulfamoyl)-phenoxy]-N-pyridin-4-yl-acetamide is dissolved in 15 ml absolute tetrahydrofuran. 320 mg lithium aluminium hydride is added under nitrogen and the mixture is subsequently heated for one hour to reflux temperature. It is cooled and saturated ammonium sulfate solution is added to the reaction mixture. Insoluble material is removed by suction filtration, the filter residue is washed with ether, the filtrate is dried over sodium sulfate and evaporated. The residue is chromatographed on a silica gel column for purification (eluting agent: methylene chloride/methanol 8:2). After evaporating the column fractions, 420 mg of the title compound is obtained as an amorphous substance. FAB-MS: M+H 384.

Example 20

N-Benzyl-N-phenyl-3-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulfonamide

The title compound was prepared analogously to example 19 except that N-benzylaniline was used in step a) instead of N-methylaniline. Amorphous substance. FAB-MS: M+H 460.

Example 21N-Phenyl-3-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulfonamide

300 mg N-benzyl-N-phenyl-3-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulfonamide (example 20) is dissolved in 20 ml methanol and hydrogenated after addition of 100 mg Pd/C (10 %) catalyst. After the uptake of hydrogen has ceased, the catalyst is removed by filtration and it is evaporated. 240 mg of the title compound is obtained as an amorphous substance. FAB-MS: M+H 370.

Example 22N-Methyl-N-pyridin-2-yl-3-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulfonamide

The title compound was prepared analogously to example 19 except that N-methyl-2-aminopyridine was used in step a) instead of N-methylaniline. Amorphous substance. FAB-MS: M+H 385.

Example 23N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-2-propanesulfonamide hydrochloride

2.88 ml (22.9 mmol) chlorotrimethylsilane was added dropwise to 0.26 g (11.4 mmol) LiBH<sub>4</sub> in 50 ml tetrahydrofuran, it was stirred for 5 minutes at room temperature and 2.00 g (5.72 mmol) N-{3-

[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-2-propanesulfonamide was added in portions which had been prepared analogously to example 1. It was boiled for 30 minutes under reflux, 20 ml methanol is carefully added dropwise after cooling followed by 30 ml 2 N sodium hydroxide solution. The solvent was mostly removed in a vacuum and it was extracted with methylene chloride. It was dried, the solvent was removed in a vacuum and ethereal hydrochloric acid was added to the residue. The solvent was removed in a vacuum, the residue was ground with tert.butylmethyl ether and 1.5 g (70 %) of the title compound was obtained of Fp. 204 - 207°C.

Example 24

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-cyclopentanesulfonamide hydrochloride

was produced analogously to example 23. Fp. 129 - 134°C.

Example 25

N-Methyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-4-fluorophenylsulfonamide hydrochloride

was produced analogously to example 23. Fp. 140 - 143°C.

Example 26

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide

was produced analogously to example 1. Oil.

MS: [EI] = 383.

Example 27

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-4-tert.butylbenzenesulfonamide

was produced analogously to example 1. Oil.

MS: [EI] = 425.

Example 28

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-1,2,3,4-tetrahydronaphthalene-6-sulfonamide hydrochloride

was produced analogously to example 23. Fp. 235 - 237°C.

Example 29

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-indane-5-sulfonamide

was produced analogously to example 23 as a free base.

Fp. 140°C (decomp.).

Example 30

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-2-biphenylsulfonamide

was produced analogously to example 23 as a free base.  
Fp. 214 - 216°C.

Example 31

N-Methyl-N-{5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-4-fluorobenzenesulfonamide hydrochloride

was produced analogously to example 23. Fp. 122 - 129°C.  
The starting material N-{5-methyl-3-[(pyridin-4-ylamino-carbonyl)-methoxy]-phenyl}-4-fluorobenzene-sulfonamide (MS m/e = 429) was produced analogously to example 17.

Example 32

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-chloro-4-fluorobenzenesulfonamide hydrochloride

was produced analogously to example 23. Fp. 198 - 200°C.  
The starting material N-{5-methyl-3-[(pyridin-4-ylamino-carbonyl)-methoxy]-phenyl}-2-chloro-4-fluorobenzene-sulfonamide (MS m/e = 449) was produced analogously to example 17.

Example 33

N-Methyl-N-{5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-trifluorobenzenesulfonamide hydrochloride

was produced analogously to example 23. Fp. 203 - 207°C. The starting material N-{5-methyl-3-[(pyridin-4-ylamino-carbonyl)-methoxy]-phenyl}-2-chloro-4-fluorobenzene-sulfonamide (MS m/e = 479) was produced analogously to example 17.

Example 34

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-methylbenzenesulfonamide hydrochloride

was produced analogously to example 23. Fp. 135°C (decomp.). The starting material N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-2-methylbenzene-sulfonamide (MS m/e = 411) was produced analogously to example 17.

Example 35

N-Methyl-N-{5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-methyl-4-fluorobenzenesulfonamide hydrochloride

was produced analogously to example 23. Fp. 146°C. The starting material N-methyl-N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-2-methyl-4-fluorobenzenesulfonamide (MS m/e = 443) was produced analogously to example 17.

**Example 36**

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-methyl-4-fluorobenzenesulfonamide hydrochloride

was produced analogously to example 23. Fp. 193°C. The starting material N-{5-methyl-3-[(pyridin-4-ylamino-carbonyl)-methoxy]-phenyl}-2-methyl-4-fluorobenzene-sulfonamide (MS m/e = 429) was produced analogously to example 17.

**Example 37**

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-methyl-5-fluorobenzenesulfonamide hydrochloride

was produced analogously to example 23. Fp. 246 - 247°C. The starting material N-{5-methyl-3-[(pyridin-4-ylamino-carbonyl)-methoxy]-phenyl}-2-methyl-5-fluorobenzene-sulfonamide (MS m/e = 429; Fp. 211 - 213°C) was produced analogously to example 17.

**Example 38**

N-Methyl-N-{5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-methyl-5-fluorobenzenesulfonamide hydrochloride

was produced analogously to example 23. Fp. 165 - 166°C. The starting material N-methyl-N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-2-methyl-5-fluorobenzenesulfonamide (MS m/e = 443) was produced analogously to example 17.

**Example 39**

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-  
2,4-difluorobenzenesulfonamide hydrochloride

was produced analogously to example 23. Fp. 227 - 228°C. The starting material N-{5-methyl-3-[(pyridin-4-ylamino-carbonyl)-methoxy]-phenyl}-2,4-difluorobenzene-sulfonamide (MS m/e = 433; Fp. 194°C) was produced analogously to example 17.

**Example 40**

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-  
3,5-dimethyl-4-pyrazolesulfonamide

was produced analogously to example 23 as a free base. Fp. 121°C. The starting material N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-3,5-dimethyl-4-pyrazolesulfonamide (MS m/e = 415) was produced analogously to example 17.

**Example 41**

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-4-  
fluorobenzenesulfonamide hydrochloride

was produced analogously to example 23. Fp. 232°C. The starting material N-{5-methyl-3-[(pyridin-4-ylamino-carbonyl)-methoxy]-phenyl}-4-fluorobenzenesulfonamide (MS m/e = 415; Fp. 156 - 159°C) was produced analogously to example 17.

**Example 42**

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-fluorobenzenesulfonamide hydrochloride

was produced analogously to example 23. Fp. 263°C. The starting material N-{5-methyl-3-[(pyridin-4-ylamino-carbonyl)-methoxy]-phenyl}-2-fluorobenzenesulfonamide (MS m/e = 415) was produced analogously to example 17.

**Example 43**

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-trifluoromethylbenzenesulfonamide hydrochloride

was produced analogously to example 23. Fp. 217 - 222°C. The starting material N-{5-methyl-3-[(pyridin-4-ylamino-carbonyl)-methoxy]-phenyl}-2-trifluoromethylbenzenesulfonamide (MS m/e = 465) was produced analogously to example 17.

**Example 44**

N-Methyl-N-{5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-4-methylbenzenesulfonamide hydrochloride

was produced analogously to example 23. Fp. 180°C. The starting material N-methyl-N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-4-methylbenzenesulfonamide (MS m/e = 425) was produced analogously to example 17.

**Example 45**

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2,6-difluorobenzenesulfonamide hydrochloride

was produced analogously to example 23. Fp. 263°C. The starting material N-{5-methyl-3-[(pyridin-4-ylamino-carbonyl)-methoxy]-phenyl}-2,6-difluorobenzene-sulfonamide (MS m/e = 433; Fp. 234 - 242°C) was produced analogously to example 17.

**Example 46**

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-hydroxy-3-tert.butyl-5-methylbenzenesulfonamide hydrochloride

- a) 50 ml (100 mmol) 2 N sodium hydroxide solution was added to 27.2 g (87.0 mmol) (3-tert.butyloxy-carbonylamino-5-methylphenoxy)-acetic acid ethyl ester (example 57b) in 300 ml methanol and stirred for 3 days at room temperature. The solvent was partially removed in a vacuum, it was extracted with ethyl acetate, the aqueous phase was acidified with hydrochloric acid and extracted with ether. It was dried and the solvent was removed in a vacuum. 15.6 g (3-tert.butyloxycarbonylamino-5-methylphenoxy)-acetic acid is obtained of Fp. 120 - 122°C.
- b) This compound was reacted with 4-aminopyridine as described in example 1c) and one obtained N-(4-

pyridinyl)-(3-tert.butyloxycarbonylamino-5-methylphenoxy)-acetamide of Fp. 204 - 205°C.

- c) 25 ml trifluoroacetic acid was added to 5.00 g (14.0 mmol) of this compound, stirred for 30 minutes at room temperature, it was made alkaline with sodium hydroxide solution and the precipitate was filtered by suction. 2.93 g (78 %) N-(4-pyridinyl)-3-(amino-5-methylphenoxy)-acetamide of Fp. 163°C was obtained.
- d) This compound was reduced as described in example 23 and 3-[2-(pyridin-4-ylamino)-ethoxy]-5-methylaniline was obtained in a 50 % yield of Fp. 208°C.
- e) This compound was reacted with 2-hydroxy-3-tert.butyl-5-methylbenzenesulfonyl chloride as described in example 1a) and the title compound was obtained. Amorphous. MS + FAB: 470.

**Example 47**

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-3-benzothiophene-sulfonamide hydrochloride

was produced analogously to example 46. For this the compound obtained in example 46d) was reacted with benzothiophene-3-sulfonyl chloride. Fp. 130°C (decomp.).

**Example 48**

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzo-2,3,1-thiadiazole-4-sulfonamide hydrochloride

was produced analogously to example 46. For this the compound obtained in example 46d) was reacted with benzo-2,3,1-thiadiazole-4-sulfonyl chloride. Fp. 110°C.

**Example 49**

N-{5-Methoxy-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-4-fluorobenzenesulfonamide hydrochloride

- a) 16.0 g (115 mmol) 3-hydroxy-5-methoxyphenol (G. Rodighiero, C. Antonello, Il Farmaco, Ed. Sci. 10, 889 - 896, (1955)), 3.7 g ammonium chloride, 13.8 ml water and 24 ml concentrated ammonia were heated in a 100 ml autoclave for 12 hours to 130°C. After cooling, the contents of the autoclave were rinsed out with methanol, the solvent was removed in a vacuum, the residue was triturated with ethyl acetate, insoluble material (6.5 g) was removed by filtration, the solvent was removed in a vacuum, the oily residue was applied to a nutsch filter with silica gel and rewashed with heptane/ethyl acetate 1:1. The solvent of the filtrate was removed and 10.4 g 3-hydroxy-5-methoxyaniline was obtained as a red oil.
- b) This compound (10.4 g, 75.0 mmol) was acetylated in 100 ml methylene chloride in the presence of 0.1 g 4-dimethylaminopyridine with 100 ml acetic

anhydride for 12 hours at room temperature. The solvent was removed in a vacuum, 200 ml methanol and 20 ml saturated sodium carbonate solution was added to the residue (mainly diacetyl compound) and it was stirred for 3 hours at room temperature. The solvent was removed in a vacuum, 250 ml water was added, it was acidified with concentrated hydrochloric acid and extracted with ethyl acetate. Removal of the solvent yielded 11 g (81 %) N-(3-hydroxy-5-methoxy-phenyl)-acetamide of Fp. 126°C.

- c) This compound (11.0 g, 61.0 mmol) was alkylated in 100 ml dry dimethylformamide in the presence of 9.1 g (65 mmol) potassium carbonate with 6.9 ml (65 mmol) ethyl chloroacetate for 8 hours at 60°C. It was diluted with water, acidified with hydrochloric acid and extracted with ethyl acetate. The organic phase was extracted with water, the organic phase was dried over magnesium sulfate, filtered and the solvent was removed in a vacuum. 10.8 g (66 %) 2-(3-acetamido-5-methoxy-phenoxy)-acetic acid ethyl ester was obtained as an oil.
- d) This compound (10.8 g, 40 mmol) in 70 ml ethanol was stirred for 4 hours with 30 ml 2 N sodium hydroxide solution, the solvent was removed in a vacuum, water was added and it was acidified. The precipitate (5.5 g carboxylic acid) was filtered by suction, dissolved in 50 ml ethanol, 50 ml 10 N sodium hydroxide solution was added and boiled for 8 hours under reflux. It was acidified with concentrated hydrochloric acid, the solvent was removed in a vacuum, 100 ml methanol was added and it was stirred for 12 hours at room temperature. The solvent was removed in a vacuum, it was

digested with ethyl acetate, filtered by suction and 5.6 g 2-(3-amino-5-methoxy-phenoxy)-acetic acid methyl ester was obtained (MS, m/e = 211).

- e) 2-[3-(4-Fluorobenzenesulfonylamino)-5-methoxy-phenoxy]-acetic acid methyl ester (MS m/e = 369) was obtained from this as an oil by reaction with 4-fluorobenzenesulfonyl chloride as described in example 1a).
- f) 2-[3-(4-Fluorobenzenesulfonylamino)-5-methoxy-phenoxy]-acetic acid of Fp. 161°C was obtained from this in a yield of 95 % as described in example 1b).
- g) N-(4-Pyridinyl)-2-[3-(4-fluorobenzenesulfonylamino)-5-methoxy-phenoxy]-acetamide of Fp. 161°C was obtained from this in a yield of 58 % as described in example 1c).
- h) The title compound of Fp. 62°C was obtained from this in a yield of 76 % as described in example 23.

**Example 50**

**N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-2-chlorobenzenesulfonamide**

was produced analogously to example 1 in a yield of 58 %. Melting point 221 - 223°C.

**Example 51**

N-Methyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-chlorobenzenesulfonamide

was produced analogously to example 12 in a yield of 22 %. Melting point 188 - 190°C.

**Example 52**

N-2-Propyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide

was produced analogously to example 12 in a yield of 47 %. Oil. MS (m/e) = 411.

**Example 53**

N-Methyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-thiophenesulfonamide

was produced analogously to example 12 in a yield of 12 %. Melting point 179 - 181°C.

**Example 54**

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-1-naphthalenesulfonamide hydrochloride

was produced analogously to example 17 in a yield of 14 %. Melting point 215 - 218°C.

**Example 55**

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-thiophenesulfonamide hydrochloride

was produced analogously to example 17 in a yield of 24 %. Melting point 252 - 254°C.

**Example 56**

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-chlorobenzenesulfonamide hydrochloride

was produced analogously to example 17 in a yield of 42 %. Melting point 254 - 258°C.

**Example 57**

N-Methyl-N-{5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-1-chlorobenzenesulfonamide hydrochloride

- a) 96 g (0.78 mol) 3-hydroxy-5-methyl-aniline (F. Wessely, H. Eibel, G. Friedrich, "Monatshefte Chem. 83, 24 - 30, (1952)) in 1.2 l dioxane and 840 ml water was admixed with 420 ml 2 N sodium hydroxide solution and with 171 g (0.78 mol) ditert.butyl-dicarbonate while cooling on ice. It was stirred for 12 hours at room temperature, the solvent was removed in a vacuum, it was acidified to pH 2 - 3 while cooling on ice and extracted with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and the solvent was removed in a vacuum. 174 g (quantitative) N-(tert.butyloxy-

carbonyl)-3-hydroxy-5-methyl-aniline was obtained as an oil. MS (m/e) = 223.

- b) 132 g (0.59 mol) of this compound in 400 ml dry dimethylformamide, 90 g (0.65 mol) potassium carbonate and 69 ml (0.65 mol) ethyl chloroacetate were heated for 3 hours to 70°C. It was poured into 1 l ice water, extracted with ethyl acetate, the organic phase was dried over sodium sulfate, filtered and the solvent was removed in a vacuum. 174 g (95 %) 2-(3-tert.butyloxycarbonyl-amino-5-methyl-phenoxy)-acetic acid ethyl ester was obtained as an oil. MS (m/e) = 309.
- c) 174 g (0.562 mol) of this compound was admixed with 200 ml trifluoroacetic acid while cooling on ice, it was stirred for 2 hours at room temperature and the solvent was removed in a vacuum. 2 N hydrochloric acid was added to the residue, it was extracted with ethyl acetate, the aqueous phase was made alkaline with sodium hydroxide solution and it was extracted with ethyl acetate. The organic phase was dried with sodium sulfate, filtered and the solvent was removed in a vacuum. 87.5 g (74 %) 2-(3-amino-5-methyl-phenyloxy)-acetic acid ethyl ester was obtained as an oil. MS (m/e) = 209.
- d) As described in example 17a), this compound was reacted with 2-chlorobenzenesulfonyl chloride and 2-[3-(2-chlorobenzenesulfonylamino)-5-methyl-phenoxy]-acetic acid ethyl ester of Fp. 133 - 137°C was obtained in a yield of 56 %.

- e) This compound was methylated as described in example 12a) and N-methyl-2-[3-(2-chlorobenzene-sulfonylamino)-5-methyl-phenoxy]-acetic acid ethyl ester was obtained in a quantitative yield. Oil. MS (m/e) = 398.
- f) This compound was saponified as described in example 1b) and N-methyl-2-[3-(2-chlorobenzene-sulfonylamino)-5-methyl-phenoxy]-acetic acid was obtained in a quantitative yield. Fp. 113 - 115°C.
- g) This compound was reacted with 4-aminopyridine as described in example 1c) and 2-{3-[(2-chlorobenzenesulfonyl)-methyl-amino]-5-methyl-phenoxy}-N-pyridin-4-yl-acetamide was obtained as an oil in a yield of 68 %.
- h) This compound was reduced as described in example 1d) and the title compound was obtained in a yield of 41 %. Fp. 213 - 215°C.

**Example 58****N-Methyl-N-{5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide hydrochloride**

The compound from example 57 (0.86 g, 2 mmol) was hydrogenated in 30 ml ethanol in the presence of 0.3 g 10 % palladium on carbon at room temperature and normal pressure. Hydrogen uptake 55 ml. It was filtered and the solvent was removed in a vacuum. It was digested with ether and 0.75 g (86 %) of the title compound was obtained of Fp. 182 - 184°C.

**Example 59****N-{2-Methoxy-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide**

- a) 8.4 g (50 mmol) ethyl bromoacetate was added dropwise in an ice bath to 8.5 g (50 mmol) 2-hydroxy-4-nitroanisole and 13.8 g (100 mmol) potassium carbonate in 120 ml acetonitrile. It was stirred for 12 hours at room temperature, the solvent was removed in a vacuum, water was added to the residue and it was extracted with ethyl acetate. The organic phase was dried with sodium sulfate, filtered and the solvent was removed in a vacuum. 12.7 g (quantitative) 2-(2-methoxy-5-nitro-phenoxy)-acetic acid ethyl ester was obtained as an oil. MS (m/e) = 255.
- b) This compound (12.1 g, 47 mmol) was hydrogenated in 300 ml methanol in the presence of 5 g Raney nickel at normal pressure and room temperature. When 3.4 l hydrogen had been taken up, it was filtered and the solvent was removed in a vacuum. 10.7 g (quantitative) 2-(2-methoxy-5-amino-phenoxy)-acetic acid ethyl ester was obtained as an oil. MS (m/e) = 225.
- c) This compound (10.7 g, 47 mmol) was reacted with benzenesulfonyl chloride as described in example 1a) and 17.2 g (quantitative) 2-(2-methoxy-5-benzenesulfonylamino-phenoxy)-acetic acid ethyl ester was obtained. MS (m/e) = 413.

- d) Following the instructions of example 1b), 11.8 g (74 %) 2-(2-methoxy-5-benzenesulfonylamino-phenoxy)-acetic acid was obtained from this compound. MS (m/e) = 337.
- e) Following the instructions of example 1c), 5 g (35 %) N-(4-pyridinyl)-2-(2-methoxy-5-benzenesulfonylamino-phenoxy)-acetamide of Fp. 179°C was obtained from this compound.
- f) Following the instructions of example 23, the title compound of Fp. 188 - 189°C was obtained from this compound.

Example 60

N-{2-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide

was produced analogously to example 59 except that in step a) 2-hydroxy-4-nitrotoluene was used instead of 2-hydroxy-4-nitroanisole. This precursor was prepared as follows: 100 g 2-amino-4-nitrotoluene was stirred into 300 ml concentrated sulphuric acid at 50°C, until it was all dissolved (30 min), 2.5 kg ice was added, it was cooled to -15°C and a solution of 50 g sodium nitrite in 200 ml water was added dropwise in such a way that the temperature did not exceed 0°C. This solution was added to a mixture of 500 ml concentrated sulphuric acid and 1 l water which was boiling under reflux. It was boiled for 1 hour under reflux, allowed to stand for 12 hours and the precipitate was filtered by suction. 87.1 g (87 %) 2-hydroxy-4-nitrotoluene of Fp. 117-120°C was obtained.

- a) 2-(2-Methyl-5-nitro-phenoxy)-acetic acid ethyl ester as an oil. MS (m/e) = 239.
- b) 2-(2-Methyl-5-amino-phenoxy)-acetic acid ethyl ester as an oil. MS (m/e) = 209.
- c) 2-(2-Methyl-5-benzenesulfonylamino-phenoxy)-acetic acid ethyl ester. Fp. 78 - 83°C.
- d) 2-(2-Methyl-5-benzenesulfonylamino-phenoxy)-acetic acid. Fp. 157 - 160°C.
- e) N-(4-Pyridinyl)-2-(2-methyl-5-benzenesulfonylamino-phenoxy)-acetamide of Fp. 157 - 161°C.
- f) Title compound of Fp. 179 - 180°C.

Example 61

Benzenesulfonic acid-5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

- a) 7.1 g (50 mmol) 5-methyl-resorcinol, 10 g (100 mmol) potassium bicarbonate and 12.6 g (55 mmol) benzyl bromoacetate were boiled in 70 ml acetonitrile for 24 hours under reflux. The solvent was removed in a vacuum, water was added to the residue and it was extracted with ether, the ether phase was extracted three times with 0.1 N sodium hydroxide solution, the ether phase was dried over sodium sulfate, filtered and the solvent was removed in a vacuum. The residue (7.75 g) was separated on silica gel with isohexane/ethyl

acetate (9:1) and 4.0 g (29 %) 2-(3-hydroxy-5-methyl-phenoxy)-acetic acid benzyl ester was obtained as an oil. MS (m/e) = 272.

- b) 2.0 g (7.5 mmol) of this compound was reacted with benzenesulfonyl chloride analogously to example 1a) and 2.1 g (68 %) 2-(3-benzenesulfonyloxy-5-methyl-phenoxy)-acetic acid benzyl ester was obtained as an oil. MS (m/e) = 412.
- c) 2.0 g (5 mmol) of this compound in 150 ml methanol was hydrogenated in the presence of 0.5 g 10 % palladium on carbon for 1 hour at room temperature and normal pressure until 140 ml hydrogen had been taken up. It was filtered, ether was added and extracted three times with a sodium bicarbonate solution. The sodium bicarbonate solution was acidified with 2 N sulphuric acid, extracted with ether, dried, the solvent was removed in a vacuum and 600 mg (38 %) 2-(3-benzenesulfonyloxy-5-methyl-phenoxy)-acetic acid was obtained. MS (m/e) = 322.
- d) 0.6 g (2 mmol) of this compound was reacted with 4-aminopyridine analogously to example 1c) and N-(pyridin-4-yl)-2-(3-benzenesulfonyloxy-5-methyl-phenoxy)-acetamide was obtained (16 %). MS (m/e) = 392.
- e) The title compound was obtained from this analogously to example 23. Fp. 144 - 146°C.

**Example 62****2-Chlorobenzenesulfonic acid-5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester**

was produced analogously to example 61. Fp. 156 - 158°C.  
Intermediate steps: 2-[3-(2-Chlorobenzenesulfonyloxy)-5-methyl-phenoxy]-acetic acid: Fp. 157 - 161°C.

N-(Pyridin-4-yl)-2-[3-[2-chlorobenzenesulfonyloxy)-5-methyl-phenoxy]-acetamide. MS (m/e) = 432.

**Example 63****4-Fluorobenzenesulfonic acid-5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester**

was produced analogously to example 61 except that in step b) 4-fluorobenzenesulfonyl chloride was used.  
Fp. 161 - 163°C.

**Example 64****1-Naphthalenesulfonic acid-5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester**

was produced analogously to example 61 except that in step b) 1-naphthalenesulfonyl chloride was used.  
Fp. 95 - 99°C.

**Example 65****2-Thiophenesulfonic acid-5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester**

- a) 24.8 g (200 mmol) 5-methylresorcinol, 43.8 g (240 mmol) 2-thiophenesulfonyl chloride and 1.5 g solid sodium bicarbonate in 200 ml water were covered with a layer of 100 ml ether and the pH was kept constant at 7.2 with a dosing apparatus using saturated sodium bicarbonate solution. It was stirred for 12 hours at room temperature at pH = 7.2, the water phase was separated, the ether phase was dried with sodium sulfate, it was filtered and the solvent was removed in a vacuum. Thiophenesulfonic acid-3-hydroxy-5-methyl-phenyl ester was obtained in a quantitative yield as an oil. MS (m/e) = 270.
- b) This compound was reacted with ethyl bromoacetate analogously to example 18a and 2-[3-(2-thiophenesulfonyloxy)-5-methyl-phenoxy]-acetic acid ethyl ester was obtained. MS (m/e) = 356.
- c) 2-[3-(2-Thiophenesulfonyloxy)-5-methyl-phenoxy]-acetic acid was obtained from this compound analogously to example 1b) of Fp. 142 - 143°C.
- d) N-(Pyridin-4-yl)-2-[3-(2-thiophenesulfonyloxy)-5-methyl-phenoxy]-acetamide was obtained from this compound analogously to example 1c). Fp. 136 - 138°C.

- e) The title compound of Fp. 176°C was obtained from this compound.

Example 66

(2-Benzyloxycarbonyl-benzenesulfonic acid)-5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

- a) 5-Methylresorcinol was reacted analogously to example 61a) with ethyl bromoacetate and 2-(3-hydroxy-5-methyl-phenoxy)-acetic acid ethyl ester was obtained as an oil. MS (m/e) = 210.
- b) Analogously to example 61b), 2-[3-(2-benzyloxy-carbonyl)-benzenesulfonyloxy-5-methyl-phenoxy]-acetic acid ethyl ester (MS (m/e) = 484) was obtained from this as an oil by reaction with 2-benzyloxy-carbonyl-benzenesulfonyl chloride.
- c) This compound was saponified for 4 h at room temperature analogously to example 1b) and 63 % 2-[3-(2-benzyloxycarbonyl-benzenesulfonyloxy)-5-methyl-phenoxy]-acetic acid was obtained. MS (m/e) = 456.
- d) N-(Pyridin-4-yl)-2-[3-(2-benzyloxycarbonyl-benzenesulfonyloxy)-5-methyl-phenoxy]-acetamide was obtained from this. MS (m/e) = 532.
- e) The title compound was obtained from this analogously to example 23. MS (m/e) = 518.

**Example 67****(2-Carboxy-benzenesulfonic acid)-5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester**

2.5 g (1 mmol) of the compound from example 66 was hydrogenated in 100 ml methanolic ammonia solution in the presence of 1 g 10 % palladium on carbon at normal pressure and room temperature. It was filtered, the solvent was removed in a vacuum, the residue was triturated with isopropanol, it was filtered by suction and recrystallized from ethanol. 0.4 g (14 %) of the title compound of Fp. 189°C was obtained.

**Example 68****(2-Methyl-benzenesulfonic acid)-5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester**

was produced analogously to example 61. Fp. 152 - 154°C. Precursor: N-(pyridin-4-yl)-2-[3-(2-methyl-benzene-sulfonyloxy)-5-methyl-phenoxy]-acetamide. Fp. 158 - 160°C.

**Example 69****(2-Methoxy-benzenesulfonic acid)-5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester**

was produced analogously to example 61. Fp. 116 - 119°C. Precursor: N-(pyridin-4-yl)-2-[3-(2-methoxy-benzene-sulfonyloxy)-5-methyl-phenoxy]-acetamide. Fp. 156 - 159°C.

2156729

- 78 -

Example 70

(2-Nitro-benzenesulfonic acid)-5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

was produced analogously to example 61. Fp. 137 - 140°C.

Precursor: N-(pyridin-4-yl)-2-[3-(2-nitrobenzene-sulfonyloxy)-5-methyl-phenoxy]-acetamide.

MS (m/e) = 453.

Example 71

(2-Amino-benzenesulfonic acid)-5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

1.0 g (2.33 mmol) of the compound from example 70 was hydrogenated in 40 ml methanol in the presence of 1 g Raney nickel for 1.5 hours at room temperature and normal pressure. It was filtered, the solvent was removed in a vacuum, the residue was admixed with 25 ml tetrahydrofuran and 25 ml ether, extracted with 0.05 M sodium hydroxide solution, the organic phase was dried, filtered and the solvent was removed in a vacuum. 0.5 g (54 %) of the title compound of Fp. 168 - 171°C was obtained.

Example 72

2-Chlorobenzenesulfonic acid-5-methyl-3-[2-(N-methyl-pyridin-4-ylamino)-ethoxy]-phenyl ester

a) N-Methyl-N-(pyridin-4-yl)-2-[3-(2-chlorobenzene-sulfonyloxy)-5-methyl-phenoxy]-acetamide (MS (m/e)

= 447) was obtained by reacting 2-[3-(2-chlorobenzene-sulfonyloxy)-5-methyl-phenoxy]-acetic acid with 4-methylamino-pyridine according to example 62.

- b) The title compound of Fp. 152 - 161°C was obtained from this analogously to example 23.

Example 73

Benzenesulfonic acid-5-chloro-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

- a) 98.8 g (0.57 mol) 5-chlororesorcinol dimethyl ether and 108 ml (1.14 mol) boron tribromide in 400 ml methylene chloride were stirred for 72 hours at room temperature. It was extracted with water, the aqueous phase was extracted with n-butanol, most of the n-butanol was removed in a vacuum and it was allowed to crystallize for 12 hours at 4°C. 19.5 g (24 %) 5-chlororesorcinol of Fp. 70 - 71°C was obtained.
- b) 3.0 g (21 mmol) of this compound in 50 ml water was covered with a layer of 20 ml ether, saturated sodium bicarbonate solution was added until a pH of 5.2 was reached. 8.6 ml (21 mmol) benzenesulfonyl chloride was slowly added while keeping the pH constant, the pH was increased to 7.0 and it was stirred for 48 hours at room temperature while keeping the pH value constant. It was extracted with ether, the ether phase was extracted with 0.1 N sodium hydroxide solution, the sodium hydroxide solution was acidified with 2 N sulphuric

acid and extracted three times with ether. The solvent was removed in a vacuum and 1.7 g (28 %) benzene-sulfonic acid-3-chloro-5-hydroxy-phenyl ester was obtained. MS (m/e) = 284.

- c) This compound was reacted with ethyl bromoacetate analogously to example 18a) and 2-[3-chloro-5-(phenylsulfonyloxy)-phenoxy]-acetic acid ethyl ester was obtained in a yield of 95 %. MS (m/e) = 370.
- d) This compound was saponified analogously to example 1b) to obtain 2-[3-chloro-5-(phenylsulfonyloxy)-phenoxy]-acetic acid of Fp. 136 - 138°C in a yield of 80 %.
- e) This compound was reacted with 4-aminopyridine analogously to example 1c) and N-(pyridin-4-yl)-2-[3-chloro-5-(phenylsulfonyloxy)-phenoxy]-acetamide of Fp. 173 - 176°C was obtained in a yield of 70 %.
- f) This compound was reduced analogously to example 23) and the title compound of Fp. 144 - 146°C was obtained. Hydrochloride: Fp. 173 - 176°C.

#### Example 74

2-Chlorobenzenesulfonic acid-5-chloro-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

was produced analogously to example 73. Intermediate steps:

2156729

- 81 -

- b) 2-Chlorobenzenesulfonic acid-3-chloro-5-hydroxy-phenyl ester. Fp. 99 - 105°C.
- c) 2-[3-Chloro-5-(2-chloro-phenylsulfonyloxy)-phenoxy]-acetic acid ethyl ester as an oil.  
MS (m/e) = 405.
- d) 2-[3-Chloro-5-(2-chloro-phenylsulfonyloxy)-phenoxy]-acetic acid. Fp. 140 - 142°C.
- e) N-(Pyridin-4-yl)-2-[3-chloro-5-(2-chlorophenyl-sulfonyloxy)-phenoxy]-acetamide. Fp. 158 - 160°C.
- f) Title compound. Fp. 149 - 150°C.

Example 75

Benzenesulfonic acid-3-[2-(pyridin-4-ylamino)-ethylamino]-phenyl ester

- a) 15 g (54 mmol) benzenesulfonic acid-(3-nitro-phenyl ester) in 200 ml methanol was hydrogenated in the presence of 2.5 g 10 % palladium on carbon at normal pressure and room temperature. It was filtered and the solvent was removed in a vacuum. The residue (13 g benzenesulfonic acid-(3-amino-phenyl ester)), 4.3 g sodium acetate and 8.7 g ethyl bromoacetate in 10 ml ethanol were boiled for 12 hours under reflux. Water was added and it was extracted with ether. The ether was removed in a vacuum and 17.3 g (99 %) 2-[3-(phenyl-sulfonyloxy)-phenylamino]-acetic acid ethyl ester was obtained as an oil. MS (m/e) = 335.

- b) This compound was saponified analogously to example 1b) to form 2-[3-(phenylsulfonyloxy)-phenylamino]-acetic acid. Yield 65 %. MS (m/e) = 307.
- c) This compound was reacted with 4-aminopyridine analogously to example 1c) to form N-(pyridin-4-yl)-2-[3-(phenylsulfonyloxy)-phenylamino]-acetamide. Oil. MS (m/e) = 383.
- d) The title compound was obtained from this analogously to example 23. 0.6 g of the compound which formed as an oil was dissolved in 10 ml ethyl acetate and a solution of 220 mg cyclohexane-sulfamic acid in 10 ml ethyl acetate was added. A few drops of isopropanol were added and it was allowed to crystallize. 0.3 g of the cyclamate of the title compound of Fp. 106 - 111°C was obtained.

Example 76

Benzenesulfonic acid-3-methyl-5-[2-(pyridin-4-ylamino)-ethylamino]-phenyl ester

- a) 12.3 g (100 mmol) 3-hydroxy-5-methylaniline (see example 57) and 25.1 g (170 mmol) phthalic acid anhydride in 250 ml acetic acid were boiled for 1 hour under reflux. 250 ml water was added, it was filtered while hot, 250 ml water was added to the filtrate and it was allowed to crystallize. It was filtered, the precipitate was dissolved in 400 ml hot methanol, admixed with active charcoal, the water was removed in a vacuum and 21.7 g (86 %) 3-phthalimido-5-methyl-phenol of Fp. 170 - 175°C was obtained.

- b) Benzenesulfonic acid-3-methyl-5-phthalimido-phenyl ester was obtained from this analogously to example 1a). MS (m/e) = 393.
- c) 3.9 g (10 mmol) of this compound and 0.7 ml (15 mmol) hydrazine hydrate in 10 ml ethanol and 30 ml methylene chloride were stirred for 12 hours at room temperature, 4 ml concentrated hydrochloric acid was added, stirred for 2 hours at room temperature, filtered, the solvent was removed in a vacuum, 2 N sodium hydroxide solution was added to the residue and it was extracted with ether, the ether phase was washed with water and with saturated saline solution, the ether was removed in a vacuum and 2.5 g (96 %) benzenesulfonic acid-3-methyl-5-amino-phenyl ester was obtained. MS (m/e) = 263.
- d) 2.5 g (9.5 mmol) of this compound was reacted with tosyl chloride analogously to example 1a) and benzenesulfonic acid-3-methyl-5-(4-methylphenyl-sulfonylamino)-phenyl ester was obtained in a quantitative yield. MS (m/e) = 417.
- e) This compound was alkylated with ethyl bromoacetate analogously to example 18a) and 5 g (quantitative yield) [4-methylbenzenesulfonyl-(3-benzene-sulfonyloxy-5-methyl-phenyl)-amino]-acetic acid ethyl ester was obtained. MS (m/e) = 503.
- f) 5 g (10 mmol) of this compound in 60 ml 6 N hydrochloric acid was boiled for 6 hours under reflux. The solvent was removed in a vacuum, water was added, it was neutralized with sodium

bicarbonate, extracted with ethyl acetate, the aqueous phase was adjusted to pH 3 with 2 N hydrochloric acid and extracted with ethyl acetate. The ethyl acetate was removed in a vacuum and 2 g (62 %) (3-benzenesulfonyloxy-5-methyl-phenyl)-amino-acetic acid was obtained. MS (m/e) = 321.

- g) This compound was reacted analogously to example 1c) and N-(pyridin-4-yl)-benzenesulfonyloxy-5-methyl-phenyl)-amino-acetamide was obtained in a yield of 12 %. MS (m/e) = 397.
- h) The title compound was obtained from this compound analogously to example 23) as an oil.  
MS (m/e) = 383.

Example 77

N-{3-[2-(Pyridin-4-ylamino)-ethylamino]-phenyl}-benzenesulfonamide

- a) 13.8 g (100 mmol) 3-nitroaniline, 12.3 g sodium acetate (150 mmol) and 25 g (150 mmol) ethyl bromoacetate in 5 ml dimethylsulfoxide were heated for 48 hours to 80°C. It was poured onto 400 ml 0.5 N hydrochloric acid, 15 ml isohexane and 10 ml ether were added and it was allowed to crystallize. It was filtered and 18.7 g (84 %) 3-nitro-phenyl-amino-acetic acid ethyl ester was obtained.  
Fp. 92°C.

- b) 3-Nitro-phenylamino-acetic acid was obtained from this analogously to example 1b) in a yield of 90 %. Fp. 159 - 162°C.
- c) N-(Pyridin-4-yl)-3-nitro-phenylamino-acetamide was obtained from this analogously to example 1c) in a yield of 89 %. Fp. 196 - 198°C.
- d) 10.4 g (38 mmol) of this compound was hydrogenated in 200 ml methanol and 100 ml ethyl acetate in the presence of 10 g Raney nickel at normal pressure and at room temperature. It was filtered, the solvent was removed in a vacuum and 7.7 g (82 %) N-(pyridin-4-yl)-(3-aminophenylamino)-acetamide was obtained. MS (m/e) = 292.
- e) N-(Pyridin-4-yl)-(3-phenylsulfonylamino-phenylamino)-acetamide was obtained from this compound analogously to example 1a). MS (m/e) = 382.
- f) The title compound was obtained from this analogously to example 23) in a yield of 40 %. MS (m/e) = 368.

**Example 78**

**N-{3-[2-(Pyridin-4-ylamino)-ethylamino]-phenyl}-thiophene-2-sulfonamide**

- a) N-(Pyridin-4-yl)-[3-(thiophene-2-ylsulfonylamino)-phenylamino]-acetamide (MS (m/e) = 388) was obtained in a yield of 59 % by reaction of the

compound from example 77d) with 2-thiophene-sulfonyl chloride analogously to example 1a).

- b) The title compound was obtained from this analogously to example 23) in a yield of 24 %.  
Fp. 196 - 198°C.

Example 79

N-{3-[2-(Pyridin-4-ylamino)-ethylamino]-5-trifluoromethyl-phenyl}-benzenesulfonamide

- a) 15 g (270 mmol) iron powder was added in portions to 24.5 g (100 mmol) 3,5-dinitrobenzenetrifluoride in 180 ml boiling glacial acetic acid. It was poured onto water, extracted with ethyl acetate and the ethyl acetate phase was neutralized with solid sodium bicarbonate. It was filtered, the solvent was removed in a vacuum, the residue (26.3 g) was applied to silica gel and eluted with isohexane/ethyl acetate (8:2). 13.0 g (63 %) 3-nitro-5-trifluoromethylaniline of Fp. 80 - 84°C was obtained.
- b) 5.0 g (24 mmol) of this compound was dissolved in 20 ml sulphuric acid and 17 ml water, it was cooled to 0°C and a solution of 1.9 g (27 mmol) sodium nitrite in 10 ml water was added. The cold solution was added to 250 ml boiling, concentrated copper sulphate solution. When the formation of nitrogen had ceased, it was extracted with ether. The ether phase was extracted with 0.05 N sodium hydroxide solution, the aqueous phase was acidified with dilute sulphuric acid and it was extracted with

ether. The ether was removed in a vacuum and 3.4 g (68 %) 3-nitro-5-trifluoromethyl-phenol of Fp. 82 - 84°C was obtained.

- c) 36.7 g (600 mmol) ethanolamine and 80.7 g (550 mmol) phthalic acid anhydride in 290 ml toluene were heated for 2 hours under reflux on a water separator. After separating 9.3 ml water it was allowed to cool, filtered and 95.1 g (90 %) N-(2-hydroxyethyl)-phthalimide of Fp. 128 - 132°C was obtained.
- d) 28.8 g (150 mmol) of this compound and 42.9 g (225 mmol) tosyl chloride in 200 ml pyridine were stirred for 3 hours at room temperature, acidified with 2 N hydrochloric acid and extracted with ethyl acetate. The ethyl acetate was removed in a vacuum and 48.3 g (85 %) 4-toluenesulfonic acid-(2-phthalimidoethyl)-ester of Fp. 144 - 148°C was obtained.
- e) 1.7 g (12.5 mmol) of this compound, 2.6 g (12.5 mmol) of compound 79c) and 4.1 g potassium carbonate in 80 ml dimethylsulfoxide were stirred for 12 hours at 50°C. It was poured onto ice, extracted with ethyl acetate, the ethyl acetate was washed with 0.01 N sodium hydroxide and saturated saline solution, the ethyl acetate was removed in a vacuum and 1.9 g (40 %) N-{2-[2-(3-nitro-5-trifluoromethylphenoxy)-ethyl]}-phthalimide of Fp. 146 - 148°C was obtained.

- f) 2-(3-Nitro-5-trifluoromethyl-phenoxy)-ethylamine was obtained quantitatively from this analogously to example 76c). MS (m/e) = 250.
- g) 1.0 g (4 mmol) of this compound, 1.15 g (4.4 mmol) 4-nitro-tetrachloropyridine (M. Roberts, H. Suschitzky, J. Chem. Soc. C 1968, 2844 - 2848) and 0.48 ml (4.4 mmol) N-methylmorpholine in 20 ml dioxane were stirred for 3 hours at room temperature. Water was added, it was extracted with ethyl acetate, the ethyl acetate was washed with water and saturated saline solution, the ethyl acetate was removed in a vacuum and 1.4 g (75 %) N-(tetrachloropyridin-4-yl)-2-(3-nitro-5-trifluoromethylphenoxy)-ethylamine of Fp. 126 - 129°C was obtained.
- h) This compound was reduced analogously to step a) and N-(tetrachloropyridin-4-yl)-2-(3-amino-5-trifluoromethylphenoxy)-ethylamine of Fp. 144 - 146°C was obtained.
- i) 0.4 g (0.92 mmol) of this compound and 0.12 ml (0.92 mmol) benzenesulfonyl chloride in 5 ml pyridine were stirred for 3 hours at room temperature, acidified with 2 N hydrochloric acid, extracted with ethyl acetate, washed with saturated saline solution, the ethyl acetate was removed in a vacuum and 0.4 g N-{3-[2-(tetrachloro-pyridin-4-ylamino)-ethoxy]-5-trifluoromethyl-phenyl}-benzenesulfonamide of Fp. 139 - 143°C was obtained.
- j) 0.4 g (0.7 mmol) of this compound was hydrogenated in 50 ml methanol in the presence of 3.5 mmol

2156729

- 89 -

sodium methyrate and 0.5 g 10 % palladium on carbon at room temperature and normal pressure. It was filtered, water was added and it was extracted with ethyl acetate. The ethyl acetate was removed in a vacuum and 0.2 g of the title compound of Fp. 140 - 144°C was obtained.

Example 80

3-Methoxy-N-methyl-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulfonamide

- a) 92 g (0.4 mmol) 3,5-dinitrobenzoyl chloride and 28.4 g (0.44 mol) sodium azide in 240 ml glacial acetic acid were stirred for 8 hours at room temperature, 400 ml water was added, the precipitate was filtered and 80.8 g (85 %) 3,5-dinitrobenzoyl azide of Fp. 105°C (decomp.) was obtained.
- b) 80.8 g (0.34 mol) of this compound in 500 ml acetic anhydride was carefully heated until generation of gas starts (90 - 100°C) and it was kept at this temperature for 4 hours. The solvent was removed in a vacuum, the residue was digested with water and 136 g (quantitative) N-(3,5-dinitrophenyl)-acetamide of Fp. 163°C was obtained.
- c) 136 g (0.34 mol) of this compound was boiled for 3 h under reflux in 500 ml ethanol and 500 ml concentrated hydrochloric acid, undissolved material was removed by filtration, the filtrate was poured into 2 l water, the yellow precipitate was filtered by suction and 41.4 g (66 %) was obtained.

2156729

- 90 -

3,5-dinitroaniline was obtained. Fp. 140°C  
(decomp.).

- d) 25 g (137 mmol) of this compound was dissolved in 50 ml glacial acetic acid and 100 ml concentrated hydrochloric acid, 10.4 g (155 mmol) sodium nitrite in 20 ml water was added dropwise within 5 minutes, it was stirred for a further 15 minutes at this temperature, the brown suspension was cooled to -20°C and it was added within 15 minutes to a solution of 2.7 g copper dichloride dihydrate in 200 ml glacial acetic acid which was saturated with sulphur dioxide and cooled to 0°C. It was extracted with ethyl acetate, the ethyl acetate was removed in a vacuum and dried at  $10^{-2}$  torr. 35.4 g (97 %) dinitro-benzenesulfonyl chloride was obtained as a brown solid which was used without further purification.
- e) 4.9 g (38 %) N-methyl-N-phenyl-3,5-dinitrobenzenesulfonamide (Fp. 175 - 178°C) was obtained analogously to example 79i) from 10.2 g (38.2 mmol) of this compound and 4.5 ml (42 mmol) N-methylaniline.
- f) 3.5 g (10.4 mmol) of this compound in 31 ml 0.4 molar methanolic sodium methylate solution was boiled for 1 hour under reflux. The solvent was removed in a vacuum, the residue was digested with ethyl acetate and it was purified over a silica gel column (100 g silica gel). It was eluted with isohexane/ethyl acetate 2:1 and 2.5 g (75 %) N-methyl-N-phenyl-3-methoxy-5-nitrobenzenesulfonamide of Fp. 112°C was obtained,

- g) This compound was hydrogenated analogously to example 58) and 2.3 g N-methyl-N-phenyl-3-methoxy-5-aminobenzenesulfonamide was obtained as an oil. MS (m/e) = 292.
- h) A solution of 630 mg (9 mmol) sodium nitrite in 2 ml water was added dropwise to a suspension of 2.3 g (7.8 mmol) of this compound in 10 ml water and 5 ml concentrated sulphuric acid which had been cooled to 0°C, it was stirred for 2 hours at this temperature, urea was added, it was heated for 15 minutes to 110°C, extracted with ethyl acetate, the ethyl acetate was washed with 2 N sodium hydroxide solution, the solvent was removed in a vacuum and 300 mg (13 %) N-methyl-N-phenyl-3-methoxy-5-hydroxy-benzenesulfonamide was obtained as an oil. MS (m/e) = 293.
- i) 250 mg (0.85 mmol) of this compound was alkylated with 0.14 ml ethyl bromoacetate analogously to example 18a) and 360 mg (quantitative) [3-methoxy-5-(methyl-phenyl-sulfamoyl)-phenoxy]-acetic acid ethyl ester was obtained as an oil. MS (m/e) = 379.
- j) This compound was saponified analogously to example 1b) and 300 mg [3-methoxy-5-(methyl-phenyl-sulfamoyl)-phenoxy]-acetic acid was obtained as a viscous substance. MS (m/e) = 351.
- k) 120 mg (33 %) N-(pyridin-4-yl)-[3-methoxy-5-(methyl-phenyl-sulfamoyl)-phenoxy]-acetamide was obtained from this compound analogously to example 1c). Fp. 105°C.

- 1) 45 mg (46 %) of the title compound was obtained from 100 mg of this compound analogously to example 1d). MS (m/e) = 413.

Example 81

3-Methoxy-N-benzyl-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulfonamide

- a) N-Benzyl-N-phenyl-3,5-dinitrobenzenesulfonamide was obtained from compound 80c) and N-benzylaniline in a yield of 65 % analogously to example 80d).  
Fp. 200°C.
- b) N-Benzyl-N-phenyl-3-methoxy-5-nitrobenzenesulfonamide was obtained from this in a quantitative yield analogously to example 80e).  
Fp. 142°C.
- c) N-Benzyl-N-phenyl-3-methoxy-5-aminobenzene-sulfonamide was obtained from this analogously to 79a) in a 56 % yield as a viscous substance.  
MS (m/e) = 368.
- d) N-Benzyl-N-phenyl-3-methoxy-5-hydroxy-benzenesulfonamide was obtained from this analogously to example 80g). MS (m/e) = 369.
- e) [3-Methoxy-5-(benzyl-phenyl-sulfamoyl)-phenoxy]-acetic acid ethyl ester was obtained from this analogously to example 18a) in a yield of 30 %.  
MS (m/e) = 455.

2156729

- 93 -

- f) [3-Methoxy-5-(methyl-phenyl-sulfamoyl)-phenoxy]-acetic acid was obtained quantitatively from this analogously to example 1b). MS (m/e) = 427.
- g) N-(Pyridin-4-yl)-[3-methoxy-5-(methyl-phenyl-sulfamoyl)-phenoxy]-acetamide was obtained from this analogously to example 1c) in a yield of 42 %. Fp. 175°C.
- h) The title compound was obtained from this analogously to example 1d) in a 50 % yield as an amorphous powder. MS (m/e) = 489.

Example 82

3-Methoxy-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulfonamide

60 mg (0.12 mmol) of the compound from example 81) was hydrogenated analogously to example 58) and 20 mg (40 %) of the title compound was obtained as an amorphous powder. MS (m/e) = 399.

Example 83

N-Methyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-5-methoxy-phenyl}-benzenesulfonamide

- a) 18.3 g (100 mmol) of the compound from 80c) was reacted with 14.3 g (110 mmol) benzenesulfonyl chloride analogously to example 79i) and 32.5 g (quant.) N-(3,5-dinitrophenyl)-benzenesulfonamide was obtained. Fp. 165°C.

- b) 44 g (136 mmol) of this compound was methylated analogously to example 12a) and 25.1 g (54 %) N-methyl-N-(3,5-dinitrophenyl)-benzenesulfonamide was obtained. Fp. 125°C.
- c) 6.8 g (20 mmol) of this compound was reduced analogously to 79a) and 6.1 g (quant.) N-methyl-N-(3-amino-5-nitro-phenyl)-benzenesulfonamide was obtained as an amorphous powder. MS (m/e) = 307.
- d) 1.8 g (30 %) N-methyl-N-(3-hydroxy-5-nitro-phenyl)-benzenesulfonamide was obtained from 6.1 g (20 mmol) of this compound as an amorphous powder analogously to example 80g). MS (m/e) = 308. (380 after silylation).
- e) 1.2 g (4 mmol) of this compound, 6 ml 1 N sodium hydroxide solution, 1.3 g tetrabutylammonium bromide, 6 ml dichloromethane and 0.4 ml iodomethane were stirred for 12 hours at room temperature. The organic phase was separated, the solvent was removed in a vacuum and the residue was purified on silica gel (150 g). It was eluted with isohexane/ethyl acetate = 2:1 and 240 mg (18 %) N-methyl-N-(3-methoxy-5-nitrophenyl)-benzenesulfonamide was obtained. Fp. 136°C.
- f) This compound was hydrogenated analogously to example 58 and N-methyl-N-(3-methoxy-5-aminophenyl)-benzenesulfonamide was obtained quantitatively as an amorphous powder. MS (m/e) = 292.

- g) N-Methyl-N-(3-methoxy-5-hydroxyphenyl)-benzenesulfonamide was obtained from this analogously to example 80g) in a 74 % yield as an amorphous powder. MS (m/e) = 293.
- h) [3-Methoxy-5-(N-methyl-phenylsulfonyl-amino)-phenoxy]-acetic acid ethyl ester was obtained from this in a yield of 89 % as an amorphous powder analogously to example 18a). MS (m/e) = 379.
- i) [3-Methoxy-5-(N-methyl-phenylsulfonyl-amino)-phenoxy]-acetic acid (74 %; MS = 351), N-(pyridin-4-yl)-[3-methoxy-5-(N-methyl-phenylsulfonyl-amino)-phenoxy]-acetamide (34 %; MS = 427) and the title compound (MS (m/e) = 413) as an amorphous powder were obtained from this analogously to examples 81f) to 81h).

**Example 84**

**3-Chloro-N-methyl-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulfonamide**

- a) The compound 80e) was reduced analogously to example 79a) and N-methyl-N-phenyl-3-amino-5-nitrobenzenesulfonamide was obtained in a 50 % yield. Fp. 175°C.
- b) A solution of 760 mg (11 mmol) sodium nitrite in 2 ml water was added dropwise to 3.5 g (10 mmol) of this compound in 40 ml 6 N hydrochloric acid at 0°C and then the suspension obtained was poured into a solution which had been prepared as follows: 3.75 g

copper sulfate pentahydrate and 1.35 g sodium chloride were dissolved in 12 ml warm water, a solution of 950 mg (7.5 mmol) sodium sulfite in 3 ml water was added dropwise, the precipitate was rapidly filtered and it was dissolved in 6 ml concentrated hydrochloric acid. It was slowly heated to 100°C, cooled, extracted with ethyl acetate and filtered over a silicic acid gel (100 g silica gel). It was eluted with isohexane/ethyl acetate and 1.45 g (43 %) N-methyl-N-phenyl-3-chloro-5-nitrobenzenesulfonamide was obtained. Fp. 143°C.

- c) This compound was reduced quantitatively analogously to example 79a) to form N-methyl-N-phenyl-3-chloro-5-aminobenzenesulfonamide. Amorphous powder. MS (m/e) = 296.
- d) The following were produced from this analogously to examples 83g) to 83i): N-methyl-N-phenyl-3-chloro-5-hydroxybenzenesulfonamide (69 %, amorphous, MS = 297); [3-chloro-5-(methyl-phenyl-sulfamoyl)-phenoxy]-acetic acid ethyl ester (92 %, amorphous, MS = 383); [3-chloro-5-(methyl-phenyl-sulfamoyl)-phenoxy]-acetic acid (quant., amorphous, MS = 355); N-(pyridin-4-yl)-[3-chloro-5-(methyl-phenyl-sulfamoyl)-phenoxy]-acetamide (32 %, amorphous, MS = 431); title compound (40 %, amorphous MS = 417).

**Example 85****3-Chloro-N-benzyl-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulfonamide**

- a) 12.3 g (46 mmol) of compound 80d) was reacted with 9.2 g (50 mmol) benzylamine analogously to example 79i) and 31.3 g (83 %) N-benzyl-N-phenyl-3,5-dinitrobenzenesulfonamide was obtained. Fp. 205°C.
- b) This compound was reduced analogously to example 79a) and N-benzyl-N-phenyl-3-amino-5-nitrobenzenesulfonamide was obtained quantitatively. Fp. 170°C.
- c) N-Benzyl-N-phenyl-3-chloro-5-nitrobenzenesulfonamide was obtained from this analogously to example 84b). Fp. 160°C.
- d) The following compounds were produced analogously to examples 84c) to 84d): N-benzyl-N-phenyl-3-chloro-5-aminobenzenesulfonamide (quant., amorphous, MS = 372); N-benzyl-N-phenyl-3-chloro-5-hydroxy-benzenesulfonamide (quant., amorphous, MS = 373); [3-chloro-5-(benzyl-phenyl-sulfamoyl)-phenoxy]-acetic acid ethyl ester (15 %, oil, MS = 459; [3-chloro-5-(benzyl-phenyl-sulfamoyl)-phenoxy]-acetic acid (50 % amorphous, MS = 431); N-(pyridin-4-yl)-[3-chloro-5-(benzyl-phenyl-sulfamoyl)-phenoxy]-acetamide (44 %, amorphous, MS = 507); title compound (40 %, amorphous, MS = 493).

**Example 86****3-Chloro-N-benzyl-N-phenyl-5-[2-(pyridin-4-ylamino)-ethylamino]-benzenesulfonamide**

The following compounds were produced from N-benzyl-N-phenyl-3-chloro-5-aminobenzene-sulfonamide (example 85d) analogously to examples 83h) to 83i): [3-chloro-5-(benzyl-phenyl-sulfamoyl)-phenylamino]-acetic acid ethyl ester (18 %, oil, MS = 458); [3-chloro-5-(benzyl-phenyl-sulfamoyl)-phenylamino]-acetic acid (quant., amorphous, MS = 430); N-(pyridin-4-yl)-[3-chloro-5-(benzyl-phenyl-sulfamoyl)-phenylamino]-acetamide (25 %, amorphous, MS = 506); title compound (50 %, amorphous, MS = 492).

**Example 87****N-Methyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide**

- a) N-Methyl-N-(3-amino-5-nitro-phenyl)-benzene-sulfonamide (example 83c) was reacted analogously to example 84b) to form N-methyl-N-(3-chloro-5-nitrophenyl)-benzenesulfonamide (52 %, amorphous, MS (m/e) = 326).
- b) This compound was reduced analogously to example 79a) to form N-methyl-N-(3-chloro-5-aminophenyl)-benzenesulfonamide (42 %, oil, MS = 296); [3-chloro-5-(N-methyl-phenylsulfonylamino)-phenoxy]-acetic acid ethyl ester (89 %, amorphous,

2156729

- 99 -

MS (m/e) = 383); [3-chloro-5-(N-methyl-phenyl-sulfonyl-amino)-phenoxy]-acetic acid (88 %; MS = 355); N-(pyridin-4-yl)-[3-chloro-5-(N-methyl-phenylsulfonyl-amino)-phenoxy]-acetamide (28 %; MS = 431) and the title compound (56 %) as an amorphous powder. MS (m/e) = 417.

Example 88

N-Benzyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-5-chloro-phenyl}-benzenesulfonamide

- a) The compound of example 83a) was benzylated with benzyl bromide analogously to example 92c) and N-benzyl-N-(3,5-dinitrophenyl)-benzenesulfonamide was obtained (quant.). Fp. 170°C.
- b) This compound was reduced analogously to 79a) and 27 % N-benzyl-N-(3-amino-5-nitrophenyl)-benzenesulfonamide was obtained as an amorphous powder. MS (m/e) = 383.
- c) N-Benzyl-N-(3-chloro-5-nitrophenyl)-benzenesulfonamide was obtained from this compound analogously to example 84b) in a 45 % yield. Fp. 148°C.
- d) This compound was reduced analogously to example 79a) and 34 % N-benzyl-N-(3-chloro-5-aminophenyl)-benzenesulfonamide was obtained. Fp. 145°C.
- e) The following compounds were obtained from this analogously to examples 83g) to 83i): N-benzyl-N-

(3-chloro-5-hydroxyphenyl)-benzenesulfonamide (quant., amorphous, MS (m/e) = 373); [3-chloro-5-(N-benzyl-phenylsulfonyl-amino)-phenoxy]-acetic acid ethyl ester (quant., amorphous, MS (m/e) = 459); [3-chloro-5-(N-benzyl-phenylsulfonyl-amino)-phenoxy]-acetic acid (82 %, Fp. 180°C (decomp.)); N-(pyridin-4-yl)-[3-chloro-5-(N-benzyl-phenylsulfonyl-amino)-phenoxy]-acetamide (54 %; Fp. 178°C) and the title compound as an amorphous powder. MS (m/e) = 493.

**Example 89**

**N-{3-[2-Pyridin-4-ylamino)-ethylamino]-5-bromophenyl}-benzenesulfonamide**

- a) A solution of 7.6 g (110 mmol) sodium nitrite in 15 ml water was added dropwise within 15 minutes to 18.3 g (100 mmol) 3,5-dinitroaniline (example 80c) in 100 ml glacial acetic acid and 100 ml 47 % aqueous hydrobromic acid at 0°C and the further procedure was as described in example 84b). 21.7 g (88 %) 3,5-dinitrobromobenzene was obtained. Fp. 65°C.
- b) This compound was reduced analogously to example 79a) and 17.4 g (91 %) 3-bromo-5-nitroaniline was obtained. Fp. 105°C.
- c) This compound was alkylated analogously to example 18a) and 3-bromo-5-nitrophenylamino-acetic acid ethyl ester was obtained quantitatively. Amorphous MS (m/e) = 303.

- d) This compound was saponified analogously to example 1b) and bromo-5-nitro-phenylamino acetic acid was obtained (22 %, amorphous, MS (m/e) = 274).
- e) This compound was reacted analogously to example 1c) and N-(pyridin-4-yl)-(3-bromo-5-nitro-phenyl-amino)-acetamide was obtained in a 29 % yield.  
Fp. 240°C.
- f) This compound was hydrogenated analogously to example 58) and N-(pyridin-4-yl)-(3-bromo-5-amino-phenyl-amino)-acetamide was obtained quantitatively. Amorphous. MS (m/e) = 321.
- g) N-(Pyridin-4-yl)-[3-bromo-5-benzenesulfonylamino-phenyl-amino)-acetamide was obtained from this.  
Amorphous. MS (m/e) = 460.
- h) The title compound was obtained from this analogously to example 1d). Amorphous.  
MS (m/e) = 446.

Example 90

Benzenesulfonic acid-3-ethyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

- a) 20 g 3,5-dimethoxybenzoic acid (110 mmol) in 80 ml thionyl chloride was boiled for 1 hour under reflux. The solvent was removed in a vacuum, the residue was taken up in 500 ml dry methylene chloride and dry ammonia was passed for 90 min over the ice-cooled solution. It was stirred for a

further 2 hours at room temperature, the solvent was removed in a vacuum, the residue was stirred for 12 hours in 200 ml water and 50 ml saturated sodium bicarbonate solution, filtered, the precipitate was dissolved in ethyl acetate, filtered over active charcoal and the ethyl acetate was removed until crystallization begun. 10.8 g 3,5-dimethoxybenzamide was obtained. Fp. 145°C.

- b) 19.5 ml (310 mmol) iodomethane in 30 ml ether was added dropwise to 7.6 g (310 mmol) magnesium in 10 ml dry ether, it was boiled for 30 min under reflux and then 11.6 g (63 mmol) 3,5-dimethoxybenzamide was added in portions. It was boiled for 22 h under reflux, 125 ml 6 N hydrochloric acid was added dropwise while cooling on ice, it was stirred for 16 hours at room temperature, the organic phase was washed with water, the solvent was removed in a vacuum and 9.4 g 3,5-dimethoxyacetophenone was obtained as an oil. MS (m/e) = 180.
- c) 9.4 g (52 mmol) of this compound in 150 ml ethanol and 2 ml concentrated hydrochloric acid was hydrogenated in the presence of 1 g palladium at 50°C and 5 bar pressure. It was filtered, the solvent was removed in a vacuum and 6.8 g (78 %) 3,5-dimethoxy-ethylbenzene was obtained as an oil. MS (m/e) = 166.
- d) 6.8 g (41 mmol) of this compound in 65 ml glacial acetic acid and 25 ml concentrated 47 % hydrobromic acid were boiled for 4 hours under reflux. The solvent was removed in a vacuum, water was added to the residue, it was extracted with ethyl acetate,

the ethyl acetate was washed with water, the solvent was removed in a vacuum and the residue was filtered over silica gel (isohexane/ethyl acetate = 3:1). 3.9 g (69 %) 5-ethyl-resorcinol was obtained as an oil. MS (m/e) = 138.

- e) 3.9 g (28 mmol) of this compound and 4.3 ml (33 mmol) benzenesulfonyl chloride in 30 ml ether and 60 ml saturated sodium bicarbonate solution were stirred for 48 hours at room temperature. The ether phase was separated, the solvent was removed in a vacuum, the residue was filtered over silica gel (isohexane/ethyl acetate 3:1) and 5.4 g (69 %) benzenesulfonic acid-3-hydroxy-5-ethyl-phenyl ester was obtained as an oil. MS (m/e) = 278.
- f) The following compounds were obtained from this analogously to examples 81e) to 81h): (3-benzene-sulfonyloxy-5-ethyl-phenyloxy)-acetic acid ethyl ester (77 %, oil, MS (m/e) = 364); (3-benzene-sulfonyloxy-5-ethyl-phenyloxy)-acetic acid (59 %, amorphous, MS (m/e) = 336); N-(pyridin-4-yl)-(3-benzenesulfonyloxy-5-ethyl-phenyloxy)-acetamide (70 %, amorphous, MS (m/e) = 412); title compound (10 %, Fp. 136°C).

#### Example 91

#### N-Benzyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-benzenesulfonamide

- a) 107 g (1 mol) para-toluidine was reacted with p-tosyl chloride analogously to example 79i) and 280 g (quant.) N-(4-methylphenyl)-4-methyl-benzene-

sulfonamide was obtained as an oil which was reacted without further purification. Crystals from ether of Fp. 105°C.

- b) 21 g (80 mmol) of this compound was added to 56 ml fuming nitric acid, 32 ml concentrated sulphuric acid was slowly added dropwise, it was poured onto ice, the precipitate was washed with water and 46.6 g (73 %) yellow solid of Fp. 170°C was obtained which was heated for 10 minutes to 100°C in 80 ml concentrated sulphuric acid, it was poured onto ice water and extracted with ethyl acetate. The solvent was removed in a vacuum and 20 g (88 %) 2,6-dinitro-4-methylaniline of Fp. 171°C was obtained.
- c) 800 ml glacial acetic acid was added to 20.5 g (300 mmol) sodium nitrite in 220 ml sulphuric acid and 53.5 g (270 mmol) 2,6-dinitro-4-methylaniline was added in portions, it was stirred for 3 hours at 40°C until all had dissolved and this solution was added dropwise to an ice-cooled suspension of 20 g copper oxide in ethanol, the solvent was removed in a vacuum, water was added and it was extracted with ethyl acetate. This preparation was carried out again for a second time and a total of 88 g (88 %) 3,5-dinitrotoluene was obtained as an amorphous powder.
- d) 88 g (480 mmol) of this compound in 520 ml methanol was saturated with 53 g ammonia and hydrogen sulphide was passed in for 15 minutes during which the temperature increased to 52°C. It was boiled for 30 minutes under reflux, 1 l water was added

and 60.5 g (82 %) 3-methyl-5-nitroaniline was obtained. Fp. 97°C.

- e) N-(3-Methyl-5-nitrophenyl)-benzenesulfonamide (quantitative) was obtained from this analogously to example 79i). Fp. 165°C.
- f) N-Benzyl-N-(3-methyl-5-nitrophenyl)-benzenesulfonamide (83 %) Fp. 154°C and N-benzyl-N-(3-methyl-5-aminophenyl)-benzenesulfonamide (34 %, amorphous, MS (m/e) = 352) were obtained from this analogously to examples 88a) to 88b).
- g) The following compounds were obtained from this analogously to examples 81e) to 81h): [3-(benzenesulfonyl-benzyl-amino)-5-methyl-phenylamino]-acetic acid ethyl ester (quant., oil, MS (m/e) = 438); [3-(benzenesulfonyl-benzyl-amino)-5-methyl-phenylamino]-acetic acid (90 %, amorphous, MS (m/e) = 410); N-(pyridin-4-yl)-[3-(benzenesulfonyl-benzyl-amino)-5-methyl-phenylamino]-acetamide (10 %, amorphous, MS (m/e) = 486); title compound (47 %, amorphous, MS (m/e) = 472).

**Example 92**

(Benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetic acid ethyl ester

- a) 100 g 4-nitrotetrachloropyridine and 50.6 ml ethanolamine in 1.2 l dioxane were stirred for 90 minutes at room temperature, the solvent was removed in a vacuum, water was added to the

residue, it was extracted with ethyl acetate, the ethyl acetate was washed with water, the solvent was removed in a vacuum and 105 g (72 %) 4-(2-hydroxyethylamino)-tetrachloropyridine was obtained. Fp. 131 - 133°C.

- b) 36.3 g (130 mmol) of this compound and 12.1 ml (170 mmol) acetyl chloride in 450 ml glacial acetic acid were stirred for 12 hours at room temperature, poured onto ice, neutralized with concentrated ammonia, extracted with ethyl acetate, the ethyl acetate was washed with water, the solvent was removed in a vacuum and 41.6 g (99 %) acetic acid-2-(tetrachloropyridin-4-ylamino)-ethyl ester was obtained. Fp. 72 - 75°C.
- c) A suspension of 10.8 g sodium hydride in 150 ml dimethylformamide was added to 109 g (340 mmol) of this compound in 700 ml dry dimethylformamide and subsequently a solution of 54 ml benzyl bromide in 350 ml dimethylformamide was added dropwise at 10°C. It was stirred for 2 hours at room temperature, poured onto 7 l ice water, filtered, the precipitate was washed with water, dissolved in 800 ml methanol and 200 ml dichloromethane, it was concentrated until crystallization began and allowed to crystallize. 120 g acetic acid-2-(benzyl-tetrachloropyridin-4-ylamino)-ethyl ester was obtained. Fp. 97 - 100°C.
- d) Enough dimethylformamide was added to 108 g (260 mmol) of this compound in 1.2 l ethanol and 390 ml 2 N sodium hydroxide solution to dissolve it all (ca. 0.5 l). It was stirred for 12 hours at

room temperature, the solvent was removed in a vacuum (finally at  $10^{-2}$  torr), 3 l water was added to the residue and it was extracted with 1 l ethyl acetate, the ethyl acetate was washed with 3 l water, the solvent was removed in a vacuum and 99 g (quant.) N-benzyl-N-(2-hydroxyethyl)-N-(tetrachloropyridin-4-yl)-amine was obtained as an oil. MS (m/e) = 366.

- e) 73 ml (520 mmol) triethylamine was added to 107 g (290 mmol) of this compound in 800 ml dichloromethane, it was cooled to 0°C and a solution of 67.1 g (350 mmol) 4-toluenesulfonyl chloride in 500 ml dichloromethane was added dropwise. The solution was stored for 16 hours at 4°C, water was added, the organic phase was separated and the solvent was removed in a vacuum. 90.6 g (64 %) 4-toluenesulfonic acid-2-(benzyl-tetrachloropyridin-4-ylamino)-ethyl ester was obtained. Fp. 114 - 116°C.
- f) 57.2 g (240 mmol) of this compound, 64.8 g (260 mmol) 3-phthalimido-5-methylphenol (example 76a) and 66.2 g (480 mmol) potassium carbonate in 1.15 l dimethylsulfoxide were stirred for 72 hours at room temperature, poured onto 3 l water, filtered, the residue was digested with diisopropyl ether and 63 g (38 %) N-benzyl-N-(tetrachloropyridin-4-yl)-N-[2-(3-phthalimido-5-methylphenoxy)-ethyl]-amine was obtained. Fp. 142 - 144°C.
- g) 19.1 g (31.8 mmol) of this compound, 2.3 ml (47.6 mmol) hydrazine hydrate and 50 ml ethanol in

100 ml dichloromethane were stirred for 12 hours at room temperature, the solvent was removed in a vacuum, the residue was suspended in 150 ml 2 N sodium hydroxide solution, extracted with dichloromethane, the organic phase was washed with water, the solvent was removed in a vacuum, the residue was digested with methanol and 11.5 g (77 %) N-benzyl-N-(tetrachloropyridin-4-yl)-N-[2-(3-amino-5-methyl-phenoxy)-ethyl]-amine was obtained. Fp. 91 - 93°C.

- h) 11.5 g (25.5 mmol) of this compound was reacted analogously to example 79i) with 3.51 ml (27.0 mmol) benzenesulfonyl chloride and 13.7 g (91 %) N-{3-[2-(benzyl-tetrachloropyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-benzenesulfonamide was obtained. Fp. 147 - 149°C.
- i) 3.0 g (4.00 mmol) of this compound in 15 ml dry dimethylformamide was added to 147 mg (6.38 mmol) sodium hydride in 2 ml dimethylformamide and 0.6 ml (5.4 mmol) ethyl bromoacetate was added dropwise. It was poured onto 300 ml water, extracted with ethyl acetate, the organic phase was washed with water, the solvent was removed in a vacuum and 3.15 g (91 %) (benzenesulfonyl-{3-methyl-5-[2-(benzyl-tetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetic acid ethyl ester was obtained. Fp. 141 - 142°C.
- j) 3.15 g (4.5 mmol) of this compound, 50 ml trifluoroacetic acid and 6.8 ml 1,2,3-trimethylbenzene were stirred for 12 hours at room temperature, poured onto ice water, neutralized

with concentrated ammonia, extracted with ether, the ether phase was washed with water, the solvent was removed in a vacuum, the residue was filtered over silica gel (ethyl acetate/isohexane 1:2.5) and 2.50 g (91 %) (benzenesulfonyl-{3-methyl-5-[2-(tetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetic acid ethyl ester was obtained as an oil. MS (m/e) = 605.

- k) 3.5 g (5.76 mmol) of this compound and 4.0 g potassium carbonate in 40 ml tetrahydrofuran and 40 ml methanol were hydrogenated in the presence of 1.0 g 10 % palladium on carbon at 4 bar pressure. It was filtered after 48 hours, the solvent was removed in a vacuum, it was filtered over silica gel (methylene chloride/methanol = 4:1) and 2.1 g (78 %) of the title compound was obtained. Amorphous. MS (m/e) = 469.

**Example 93**

(Benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetic acid

1.20 g (2.55 mmol) of the compound of example 92) was saponified in 20 ml ethanol with 5.1 ml 1 N sodium hydroxide solution for 2 hours at 45°C. It was neutralized with 1 N hydrochloric acid, the solvent was removed in a vacuum, the residue was taken up in 20 ml water and it was allowed to crystallize. 0.97 g (86 %) of the title compound was obtained. Fp. 100 - 102°C (decomp.)

**Example 94**

(Benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

1.5 g (3.2 mmol) of the compound of example 92) was dissolved in 12 ml concentrated ammonia and 30 ml methanol. After 12 hours at room temperature, it was filtered and 0.99 g (70 %) of the title compound was obtained. Fp. 163 - 165°C.

**Example 95**

N-(2-Hydroxyethyl)-(benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in a yield of 60 % analogously to example 94 using ethanolamine instead of ammonia. Fp. 169 - 170°C.

**Example 96**

N-(3-Hydroxyethyl)-(benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in a yield of 70 % analogously to example 94 using 3-propanolamine instead of ammonia. Fp. 148 - 152°C.

**Example 97**

N-Methyl-(benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in a yield of 58 % analogously to example 94 using a 25 % ethanolic methylamine solution instead of ammonia. Fp. 136 - 140°C.

**Example 98**

N,N-Dimethyl-(benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in a yield of 38 % analogously to example 94 using a 41 % ethanolic dimethylamine solution instead of ammonia. Amorphous. MS (m/e) = 468.

**Example 99**

N-(2-Aminoethyl)-(benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in a yield of 45 % analogously to example 94 using ethylenediamine instead of ammonia. Amorphous. MS (m/e) = 483.

Exempl 100

N-(2-Aminoethyl)-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-amino)-benzenesulfonamide

The compound of example 94) was reduced analogously to example 18c) and the title compound was obtained in a yield of 34 %. Amorphous MS (m/e) = 426.

Example 101

N-(2,3-Dihydroxypropyl)-(benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in a yield of 40 % analogously to example 94 using 2,3-dihydroxypropylamine instead of ammonia. Fp. 148 - 151°C.

Example 102

N-(2,3-Dihydroxypropyl)-N-{3-[2-pyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-benzenesulfonamide

- a) 10.0 g (75.7 mmol) 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane and 14.3 g (75 mmol) 4-toluene-sulfonic acid chloride in 7 ml pyridine were stirred for 16 hours at room temperature, poured onto 200 ml water, extracted with ethyl acetate and the solvent was removed in a vacuum. It was crystallized from isohexane and 10.3 g (48 %) 4-methylbenzenesulfonic acid-(2,2-dimethyl-1,3-dioxolan-4-yl-methyl) ester was obtained. Fp. 45 - 47°C.

- b) 0.24 g (0.83 mmol) of this compound was added to a solution of 23 mg sodium hydride and 0.46 g (0.75 mmol) of the compound of example 92h) in 3 ml dimethylformamide, it was stirred for 8 hours at 110°C, poured onto water, extracted with ethyl acetate, the solvent was removed in a vacuum and 300 mg (55 %) N-(2,2-dimethyl-1,3-dioxolan-4-yl-methyl)-N-{3-[2-(benzyl-tetrachloropyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-benzene-sulfonamide was obtained as an oil. MS (m/e) = 725.
- c) N-(2,3-Dihydroxypropyl)-N-{3-[2-(benzyl-tetrachloropyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-benzene-sulfonamide (38 %, Fp. 133 - 136°C) was obtained from this compound analogously to example 92j).
- d) The title compound (66 %, amorphous, MS (m/e) = 457) was obtained from this compound analogously to example 96k).

**Example 103**

**4-(Benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-butyric acid ethyl ester**

The following compounds were obtained analogously to examples 92i) to 92k) by using ethyl 4-bromobutyrate in example 92i) instead of ethyl bromoacetate: 4-(benzenesulfonyl-{3-methyl-5-[2-(benzyl-tetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-butyric acid ethyl ester (78 %, Fp. 106 - 108°C); 4-(benzenesulfonyl)-{3-methyl-5-[2-(tetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-butyric acid ethyl ester (oil, MS (m/e) = 633);

title compound (75 %, amorphous, MS (m/e) = 497).

**Example 104**

5-(Benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-pentanoic acid ethyl ester

The following compounds were obtained analogously to examples 92i) to 92k) by using ethyl 5-bromopentanoate in example 92i) instead of ethyl bromoacetate:

5-(benzenesulfonyl-{3-methyl-5-[2-(benzyl-tetrachloro-pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-pentanoic acid ethyl ester (72 %, Fp. 90 - 91°C); 5-(benzenesulfonyl-{3-methyl-5-[2-(tetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-pentanoic acid ethyl ester (86 %, oil, MS (m/e) = 647); title compound (78 %), amorphous, MS (m/e) = 511).

**Example 105**

6-(Benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-hexanoic acid ethyl ester

The following compounds were obtained analogously to examples 92i) to 92k) by using ethyl 6-bromohexanoate in example 92i) instead of ethyl bromoacetate: 6-(benzenesulfonyl-{3-methyl-5-[2-(benzyl-tetrachloro-pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-hexanoic acid ethyl ester (75 %, oil, MS (m/e) = 751); 6-(benzenesulfonyl-{3-methyl-5-[2-(tetrachloro-pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-hexanoic acid ethyl ester (49 %, oil, MS (m/e) = 661); title compound (56 %, amorphous, MS (m/e) = 525).

**Example 106**

4-(Benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-butyric acid

was obtained analogously to example 93) from the compound of example 103). 65 % yield, amorphous, MS (m/e) = 469.

**Example 107**

5-(Benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-pentanoic acid

was obtained analogously to example 93) from the compound of example 104). 53 % yield, Fp. 117 - 120°C.

**Example 108**

6-(Benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-hexanoic acid

was obtained analogously to example 93) from the compound of example 105). 53 % yield, amorphous, MS (m/e) = 498.

**Example 109**

2-Methoxy-benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetic acid ethyl ester

The following compounds were obtained analogously to

examples 92h) to 92k) by using 2-methoxybenzenesulfonyl chloride in step 92h) instead of benzenesulfonyl chloride: 2-methoxy-N-{3-[2-benzyl-tetrachloropyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-benzene-sulfonamide (65 %, Fp. 175°C); (2-methoxy-benzene-sulfonyl-{3-methyl-5-[2-(benzyl-tetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetic acid ethyl ester (91 %, Fp. 128 - 130°C); (2-methoxybenzenesulfonyl-{3-methyl-5-[2-(tetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetic acid ethyl ester (89 %, Fp. 126°C); title compound (81 %, Fp. 58 - 63°C).

**Example 110**

2-Methoxy-benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetic acid

was obtained from the compound of example 109) analogously to example 93). 82 %, Fp. 218 - 222°C.

**Example 111**

(2-Methoxy-benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained analogously to example 94) from the compound of example 109. (63 %, Fp. 205°C).

Example 112

N-(2-Hydroxyethyl)-(2-methoxy-benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in a yield of 93 % analogously to example 95) from the compound of example 109. Fp. 175°C.

Example 113

N-(3-Hydroxypropyl)-(2-methoxy-benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in a yield of 95 % analogously to example 96 from the compound of example 109. Fp. 165 - 167°C.

Example 114

N-Methyl-(2-methoxy-benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in a yield of 96 % analogously to example 97 from the compound of example 109. Amorphous.

MS (m/e) = 484.

Example 115

N,N-Dimethyl-(2-methoxy-benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in a yield of 73 % analogously to example 98 from the compound of example 109. Amorphous,  
MS (m/e) = 498.

Example 116

N-(2-Aminoethyl)-(2-methoxy-benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in a yield of 93 % analogously to example 99 from the compound of example 109. Amorphous,  
MS (m/e) = 513.

Example 117

N-(2,3-Dihydroxypropyl)-(2-methoxy-benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in a yield of 75 % analogously to example 101 from the compound of example 109. Amorphous,  
MS (m/e) = 544.

Example 118

(2-Methoxy-benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetonitrile

250  $\mu$ l trichloroacetyl chloride in 0.5 ml dichloromethane was added at 0°C to 94 mg (0.2 mmol) of the compound of example 111) in 0.5 ml dichloromethane and 60  $\mu$ l triethylamine. After 5 minutes it was neutralized with triethylamine, the solvent was removed in a vacuum, and the residue was filtered over silica gel (ethyl acetate/ methanol ammonia = 4:1). 60 mg of the title compound was obtained as an amorphous substance.

MS (m/e) = 452.

Example 119

N-(2-Aminoethyl)-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-2-methoxy-benzenesulfonamide

(2-Methoxy-benzenesulfonyl-{3-methyl-5-[2-(benzyl-tetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetonitrile (92 %, Fp. 154°C) was obtained by reacting 2-methoxy-N-{3-[2-(benzyl-tetrachloropyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-benzenesulfonamide (example 109) with chloroacetonitrile analogously to example 92i), from which (2-methoxy-benzenesulfonyl-{3-methyl-5-[2-(tetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetonitrile was obtained analogously to example 92j) (85 %, amorphous, MS (m/e) = 588) which was reacted to form the title compound analogously to example 92k) (10 %, amorphous, MS (m/e) = 456).

**Example 120**

2-{3-[2-(Benzyl-pyridin-4-ylamino)-ethoxy]-5-methyl-phenyl-sulfamoyl}-benzoic acid methyl ester

- a) 4-Toluenesulfonic acid-2-(benzyl-tetrachloro-pyridin-4-ylamino)-ethyl ester (example 92e) was reacted with 3-nitrophenol analogously to example 92f) and N-benzyl-N-(tetrachloropyridin-4-yl)-N-[2-(3-nitro-phenoxy)-ethyl]-amine was obtained. (61 %, Fp. 120 - 122°C).
- b) This compound was reduced analogously to example 79a) and N-benzyl-N-(tetrachloropyridin-4-yl)-N-[2-(3-aminophenoxy)-ethyl]-amine was obtained (41 %, Fp. 105 - 107°C).
- c) This compound was reacted analogously to example 92h) to form N-{3-[2-(benzyl-tetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulfonamide. (78 %, Fp. 120 - 122°C).
- d) This compound was hydrogenated analogously to example 92k) and the title compound was obtained (63 %, amorphous, MS (m/e) = 517).

**Example 121**

[2-(Methyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy-phenyl]-sulfamoyl}-phenoxy)-acetic acid ethyl ester

- a) N-Benzyl-N-(tetrachloropyridin-4-yl)-N-[2-(3-amino-5-methyl-phenoxy)-ethyl]-amine (example 92g) was

reacted analogously to example 92h) with 2-benzyl-oxy-benzenesulfonyl chloride to obtain N-{3-[2-(benzyl-tetrachloropyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-2-benzyloxy-benzenesulfonamide. (55 %, Fp. 176°C).

- b) This compound was methylated analogously to example 12) and N-methyl-N-{3-[2-(benzyl-tetrachloropyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-2-benzyloxy-benzenesulfonamide was obtained (78 %, amorphous, MS (m/e) = 729).
- c) N-Methyl-N-{3-[2-(tetrachloropyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-2-hydroxy-benzene-sulfonamide was obtained from this compound analogously to example 92j) (87 %, amorphous, MS (m/e) = 549).
- d) This compound was reacted analogously to example 18) to form [2-(methyl-{3-methyl-5-[2-(tetrachloropyridin-4-ylamino)-ethoxy-phenyl]-sulfamoyl}-phenoxy)-acetic acid ethyl ester (quant. oil, MS (m/e) = 635).
- e) This compound was hydrogenated analogously to example 92k) and the title compound was obtained (50 %, amorphous, MS (m/e) = 499).

**Example 122****N-{3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-hydroxy-benzenesulfonamide**

- a) N-{3-[2-(Benzyl-tetrachloropyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-2-benzyloxybenzenesulfonamide (example 121a) was reacted analogously to example 92j) to form N-{3-[2-(tetrachloropyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-2-hydroxy-benzenesulfonamide (70 %, amorphous, MS (m/e) = 535).
- b) The title compound was obtained from this analogously to example 92k). (81 %, amorphous, MS (m/e) = 399).

**Example 123****N-Methyl-N-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-hydroxy-benzenesulfonamide**

N-Methyl-N-{3-[2-(benzyl-tetrachloropyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-2-benzyloxy-benzenesulfonamide (example 121b) was reacted analogously to example 122) to obtain N-methyl-N-{3-[2-(tetrachloropyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-2-hydroxy-benzenesulfonamide (65 %, amorphous, MS (m/e) = 549) and the title compound (27 %, amorphous, MS (m/e) = 413).

**Example 124**

[2-(Methyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-sulfamoyl)-phenoxy]-acetic acid

- a) [2-(Methyl-{3-methyl-5-[2-(tetrachloropyridin-4-ylamino)-ethoxy-phenyl]-sulfamoyl)-phenoxy]-acetic acid ethyl ester (example 121d) was saponified analogously to example 93) to obtain (2-(methyl-{3-methyl-5-[2-(tetrachloropyridin-4-ylamino)-ethoxy-phenyl]-sulfamoyl)-phenoxy]-acetic acid (94 %, amorphous, MS (m/e) = 607).
- b) The title compound was obtained from this analogously to example 92k) (75 %, amorphous, MS (m/e) = 471).

**Example 125**

N-Ethoxycarbonyl-N-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-methoxy-benzenesulfonamide

- a) 2-Methoxy-N-{3-[2-(benzyl-tetrachloropyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-benzenesulfonamide (example 109) was reacted analogously to example 92i) with ethyl chloroformate to obtain N-ethoxycarbonyl-N-{3-[2-(benzyl-tetrachloropyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-2-methoxy-benzenesulfonamide was obtained (quant. amorphous, MS (m/e) = 711).
- b) N-Ethoxycarbonyl-N-{3-[2-(tetrachloro-pyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-2-methoxy-

benzenesulfonamide was obtained from this analogously to example 92j) (80 %, Fp. 156°C).

- c) The title compound was obtained from this analogously to example 92k) (66 %, amorphous, MS (m/e) = 485).

Example 126

N-(2-Hydroxyethyl)-N-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-methoxy-benzenesulfonamide

24 mg (0.6 mmol) lithium aluminium hydride was added to 150 mg (0.3 mmol) (2-methoxy-benzenesulfonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetic acid ethyl ester (example 109) in 5 ml dry tetrahydrofuran and it was boiled for 2 hours under reflux. 1 drop of water and 3 drops of 2 N hydrochloric acid were added, it was filtered and the solvent was removed in a vacuum. The residue was filtered over 50 g silica gel (methylene chloride/methanol = 4:1) and 50 mg (36 %) of the title compound was obtained as an amorphous solid. MS (m/e) = 457.

Example 127

N-{3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-pyridin-3-sulfonamide

was obtained analogously to example 57) by using 3-pyridinesulfonyl chloride in step 57d). Amorphous. MS (m/e) = 385.

Example 128Description of pharmacological experimentsThrombin time

The thrombin time is a conventional test in clinical coagulation diagnostics. This parameter measures the action of thrombin on fibrinogen and the formation of clots. Inhibitors of thrombin result in an extended thrombin time.

In order to obtain plasma, 9 parts of fresh blood from healthy donors was mixed with one part of sodium citrate solution (0.11 mol/l) and centrifuged for 10 minutes at room temperature at ca. 3000 r.p.m.. The plasma was pipetted off and can be stored at room temperature for ca. 8 hours.

200  $\mu$ l citrate plasma was incubated for 2 minutes at 37°C in a ball coagulometer (KC10 from the Amelung Company). 10  $\mu$ l dimethylsulfoxide (DMSO) or a solution of the active substance in DMSO was added to 190  $\mu$ l pre-heated thrombin reagent (Boehringer Mannheim GmbH; contains ca. 3 U/ml horse thrombin and 0.0125 M  $\text{Ca}^{++}$ ). On addition of 200  $\mu$ l of this solution to the plasma a stopwatch was started and the time at which coagulation starts was determined. The thrombin time was ca. 24 sec. in control measurements and was substantially increased by the active substances.

The measured thrombin times in seconds are given in the following table as a difference to the control. The

concentrations of the active substances in the final volume were 250  $\mu\text{M}$  (TT250), 25  $\mu\text{M}$  (TT25) and 2.5  $\mu\text{M}$  (TT2.5).

#### Thrombin inhibition

The kinetic measurements were carried out in 0.1 M phosphate buffer that contained 0.2 M sodium chloride and 0.5 % polyethylene glycol 6000 at a pH = 7.5 and 25°C with the substrate H-(D)-Phe-Pro-Arg-pNA (S-2238 Kabi) and human  $\alpha$  thrombin (Sigma, specific activity = 2150 NIH units/mg) in polystyrene semi-microcuvettes in a total volume of 1 ml.

In a preliminary test each active substance was tested whether it inhibits thrombin rapidly or slowly. For this the reaction was firstly started by adding 0.03 NIH units thrombin to a 100  $\mu\text{M}$  solution of the substrate and the active substance. In a second experiment, substrate was added to a solution of thrombin and the active substance which had been incubated for 5 minutes. The increase in the concentration of p-nitroaniline with time was monitored spectroscopically (UV-VIS spectrophotometer Lambda-2 from the Perkin-Elmer Company) at 405 nm for 12 min. Since the measured curves obtained in both experiments were linear and parallel, the active substances of the following table are rapid thrombin inhibitors. The inhibition constants  $K_i$  were then determined as follows. The substrate was used at concentrations of 100  $\mu\text{M}$ , 50  $\mu\text{M}$ , 30  $\mu\text{M}$ , 20  $\mu\text{M}$  and at each substrate concentration a measurement was carried out without inhibitor and three measurements were carried out in the presence of various concentrations of the inhibitors listed in the following table. The

reactions were started by addition of thrombin. The increase in absorbance at 405 nm due to the formation of p-nitroaniline was monitored over a time period of 12 minutes. Measurement points (time versus absorbance) were transferred to a PC at intervals of 20 seconds. The rates  $V_0$  (change in absorbance per second; measurements without inhibitor) and  $V_i$  (measurements with inhibitor) were determined by linear regression. Only that part of the measurement was used in which the substrate concentration had decreased by less than 15 %.  $K_m$  and  $V_{max}$  were determined from a measurement series (constant inhibitor concentration, variable substrate concentrations) by a non-linear fit to the equation

$$V = \frac{V_{max}*[S]}{[S] + K_m}$$

Finally  $K_i$  was calculated from the entire series of measurements by non-linear fitting to the equation

$$V = \frac{V_{max}*[S]}{K_m*(1 + [S]/K_i) + [S]}$$

The Michaelis constant  $K_m$  was  $3.8 \pm 2 \mu M$  in all measurements.

The inhibition constants  $K_i$  of the active substances are stated in the following table in units of  $\mu M$ .

Inhibition of trypsin and plasmin

10 mg bovine pancreatic trypsin (Sigma) was dissolved in 100 ml 1 mM hydrochloric acid and stored in a refrigerator. 20  $\mu$ l of this was admixed with 980  $\mu$ l 1 mM hydrochloric acid. 25  $\mu$ l thereof was used for each measurement. The measurement was carried out as described for thrombin.  $K_m = 45 \mu M$ . The substances listed in the following table do not inhibit trypsin ( $K_i > 400 \mu M$ ).

The measurements with human plasmin (Sigma, 10 units) were carried out as described for thrombin using the substrate S-2251 (H-(D)-Val-Leu-Lys-pNA, Kabi). 0.01 units plasmin were used for each measurement.  $K_m = 250 \mu M$ . The substances listed in the following table do not inhibit plasmin ( $K_i > 400 \mu M$ ).

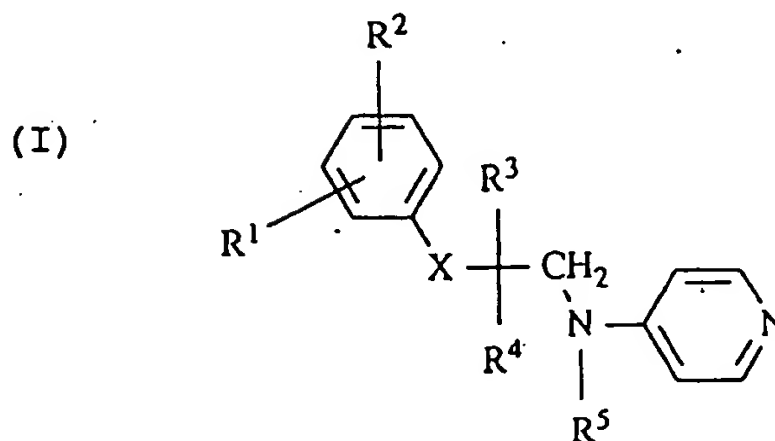
2156729

- 129 -

Example No.	K <sub>i</sub> thrombin	TT250	TT25	TT2.5
2	0.300	150	40	6
8	1.000	288	58	13
10	3.000	157	43	7
15	0.130	270	144	15
48	0.600	300	238	46
59	6.000	53	8	0
60	0.600	137	62	13
72	0.024	300	300	159
79	5.000	30	8	0
80	0.150	300	213	44
83	0.100	300	192	48
86	0.040	300	167	11
89	1.000	132	38	6
90	0.024	300	300	125
100	0.083	300	300	186
108	0.055	300	300	62
124	0.250	300	300	104
125	0.150	300	273	73

C l a i m s

1. 4-Aminopyridines of the general formula I



in which

R<sup>1</sup> signifies the group R<sup>6</sup>-SO-NR<sup>7</sup>-, R<sup>6</sup>-SO<sub>2</sub>-NR<sup>7</sup>-, R<sup>6</sup>-NR<sup>7</sup>-SO-, R<sup>6</sup>-NR<sup>7</sup>-SO<sub>2</sub>-, R<sup>6</sup>-SO-O-, R<sup>6</sup>-SO<sub>2</sub>-O-, R<sup>6</sup>-O-SO- or R<sup>6</sup>-O-SO<sub>2</sub>-,

R<sup>2</sup> signifies a hydrogen or halogen atom, a cyano, alkyl, alkoxy or haloalkyl group,

X signifies an oxygen atom, a sulphur atom or the NH group,

R<sup>3</sup> and R<sup>4</sup> are the same or different and signify hydrogen atoms or alkyl groups,

R<sup>5</sup> signifies a hydrogen atom, an alkyl group or the aralkyl group,

$R^6$  signifies an alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroarylalkyl group, whereby the aryl or heteroaryl radicals can be substituted one or more times by nitro, halogen, nitrile, hydroxyl, amino, carboxyl, alkoxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, aralkoxycarbonyl, alkyl, cycloalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxy, alkenyloxy, alkynyloxy, aralkoxy, cyanoalkyloxy, alkylthio, alkylsulphanyl, alkylsulphonyl, amino, alkylamino, dialkylamino, aralkylamino diaralkylamino, alkylsulphonylamino, alkylcarbonylamino, formylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl or by one or several of the groups  $-Y-CO_2R^8$ ,  $-S-Y-CO_2R^8$ ,  $-O-Y-CO_2R^8$ ,  $-NH-Y-CO_2R^8$ ,  $-S-Y-CONR^8R^9$ ,  $-O-Y-CO-NR^8R^9$  or  $-NH-Y-CONR^8R^9$  in which the alkyl, alkenyl or alkynyl fragments can be substituted once or several times by halogen, hydroxy, alkoxy, alkylcarbonyloxy, amino or carboxy groups,

$R^7$  denotes a hydrogen atom, an alkyl, cycloalkyl, alkenyl or alkynyl residue wherein these residues can be substituted once or several times by halogen, hydroxy, alkoxy, amino, alkylamino, dialkylamino, carboxy, alkylcarbonyl or alkoxycarbonyl, or denote an alkoxycarbonyl, cyanoalkyl, heteroaryl, aryl, aralkyl or heteroarylalkyl group in which case the aryl or heteroaryl residue can be substituted once or several times by halogen, nitrile, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, alkenyloxy, alkynyloxy, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkoxy, hydroxy, carboxy, hydroxy-

alkyl, carboxyalkyl, alkoxycarbonyl, amino, alkylamino, dialkylamino, alkylsulfonylamino, alkylcarbonylamino, formylamino, aminocarbonyl or phenyl, or denotes a  $-Y-CO_2R^8$  or  $-Y-CONR^8R^9$  group,

Y denotes a linear or branched alkylene chain,

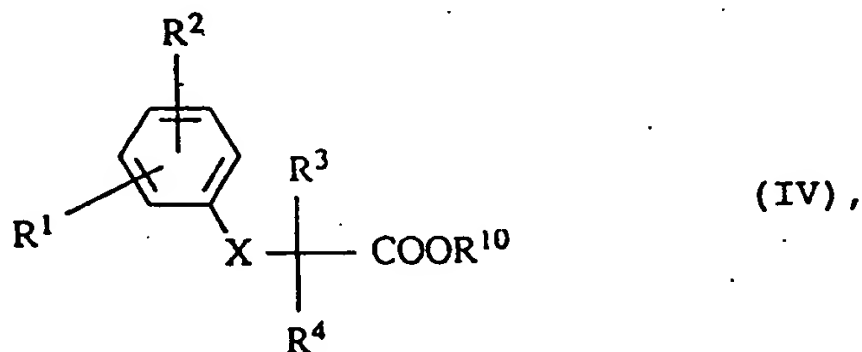
$R^8$  and  $R^9$  are the same or different and denote hydrogen atoms, aralkyl, cycloalkyl or alkyl groups, which can be substituted once or several times by halogen, hydroxy, alkoxy, alkyl-carbonyloxy, amine or carboxy, or  $R^8$  and  $R^9$  together with the N atom to which they are bound, form a saturated ring which can contain an additional oxygen, sulphur or nitrogen atom,

as well as hydrates, solvates and physiologically tolerated salts thereof, and the optically active forms, racemates and mixtures of diastereomers of these compounds.

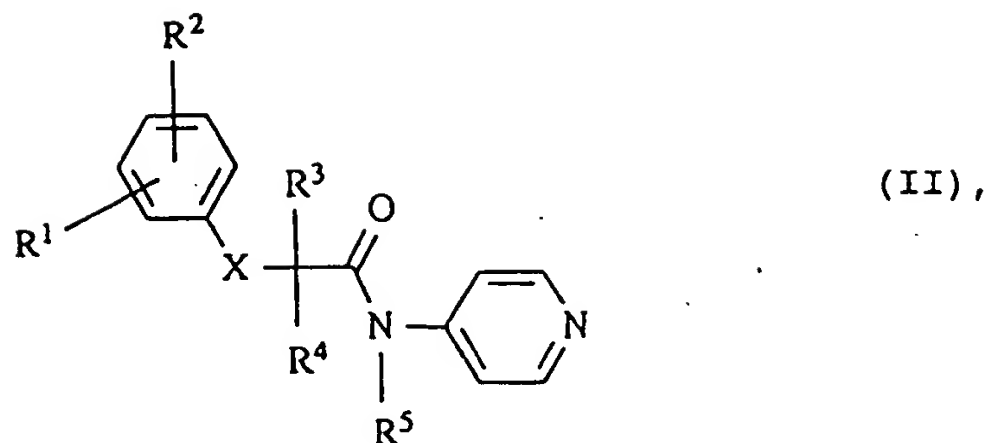
2. 4-Aminopyridines of formula I as claimed in claim 1, wherein  $R^1$  denotes  $R^6-SO-NR^7-$ ,  $R^6-NR^7-SO_2-$ ,  $R^6-SO_2-O-$  or  $R^6-O-SO_2-$ .
3. 4-Aminopyridines of formula I as claimed in claim 1 or 2, wherein  $R^2$  denotes a hydrogen, chlorine or bromine atom, or a  $C_1-C_6$  alkyl group, a  $C_1-C_6$  alkoxy group or a trifluoromethyl group.

4. 4-Aminopyridines of formula I as claimed in one of the claims 1 to 3, wherein X denotes an oxygen atom or a NH group.
5. 4-Aminopyridines of formula I as claimed in one of the claims 1 to 4, wherein R<sup>3</sup> and R<sup>4</sup> are the same or different and represent hydrogen atoms or C<sub>1</sub>-C<sub>6</sub> alkyl groups.
6. 4-Aminopyridines of formula I as claimed in one of the claims 1 to 5, wherein R<sup>5</sup> represents a hydrogen atom, a C<sub>1</sub>-C<sub>6</sub> alkyl group or a benzyl group.
7. 4-Aminopyridines of formula I as claimed in one of the claims 1 to 6, wherein R<sup>6</sup> denotes a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>3</sub>-C<sub>7</sub> cycloalkyl group, an unsubstituted phenyl or benzyl group or a phenyl or benzyl group substituted once or several times by fluorine, chlorine, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, nitro, amino, hydroxy, carboxy, benzyloxycarbonyl, C<sub>1</sub>-C<sub>6</sub> alkoxy-carbonyl, trifluoromethyl or a -O-Y-CO<sub>2</sub>R<sup>8</sup> group; a naphthyl, tetrahydronaphthyl, biphenyl or indanyl group, a thienyl, pyrazolyl or pyridyl, benzthienyl or benzothiadiazinyl group.
8. 4-Aminopyridines of formula I as claimed in one of the claims 1 to 7, wherein R<sup>7</sup> denotes a hydrogen atom, a C<sub>1</sub>-C<sub>6</sub> alkyl group, C<sub>2</sub>-C<sub>6</sub> alkenyl group or an aralkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl group, a cyanoalkyl group, a hydroxyalkyl group or an aminoalkyl group, a -Y-COR<sup>8</sup> group or a -Y-CONR<sup>8</sup>R<sup>9</sup> group.

9. 4-Aminopyridines of formula I as claimed in one of the claims 1 to 8, wherein Y denotes a methylene, propylene, butylene or pentylene group.
10. 4-Aminopyridines of the formula I according to one of claims 1 to 9, characterised in that  $R^8$  signifies a hydrogen atom or an alkyl group, a hydroxyalkyl group or an aminoalkyl group.
11. 4-Aminopyridines of the formula I according to one of claims 1 to 10, characterised in that  $R^9$  signifies a hydrogen atom or an alkyl group.
12. Process for the preparation of compounds of the formula I according to one of claims 1 to 11, characterised in that one either
  - a) saponifies a compound of the formula IV

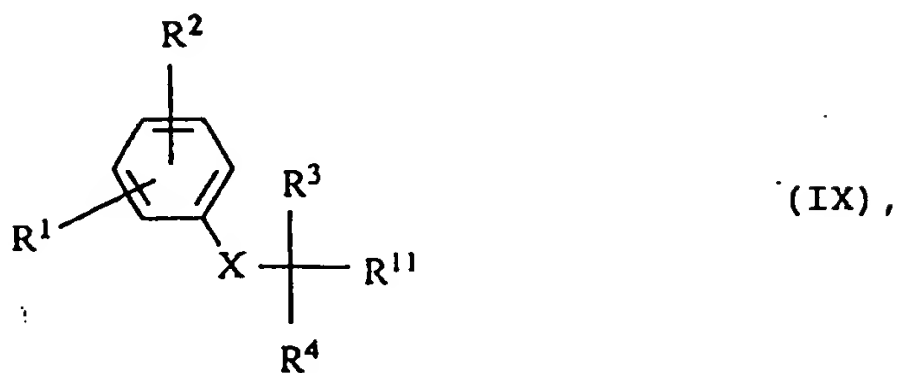


in which  $R^1$ - $R^4$  and X have the given meanings and  $R^{10}$  signifies an alkyl or benzyl group, and reacts the free acid with 4-aminopyridine to give the compound of the formula II

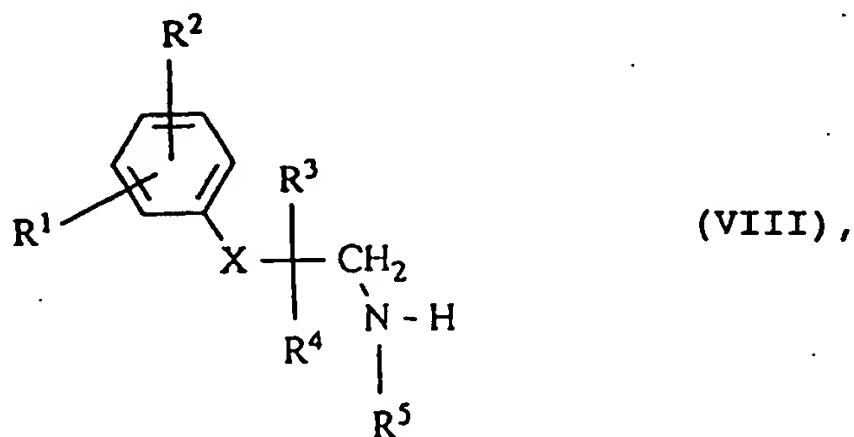


and reduces the compound of the formula II, or

b) reduces a compound of the formula IX

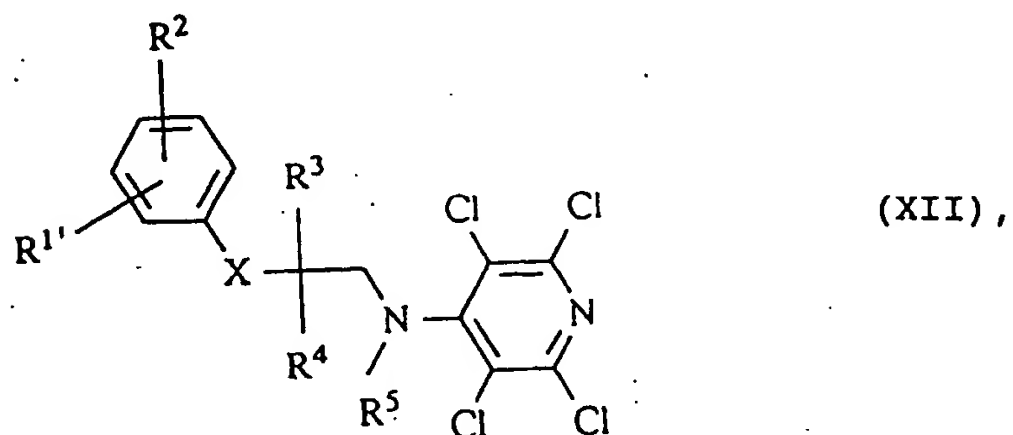


in which  $R^1$ - $R^4$  and X have the given meanings and  $R^{11}$  signifies a nitrile group or an amide group  $-\text{CONHR}^5$ , whereby  $R^5$  has the given meaning, to give the compound of the general formula VIII

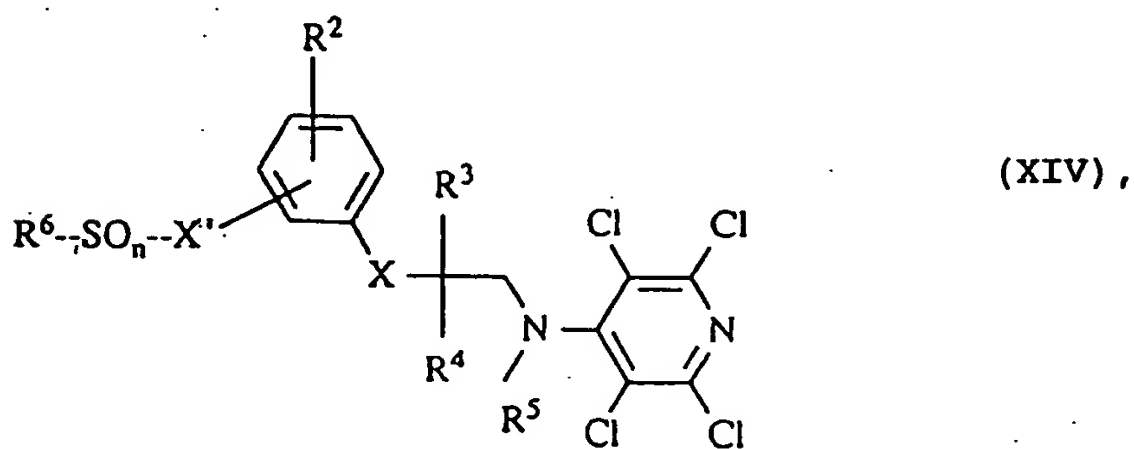


and reacts the compound obtained with a pyridine derivative which has a nucleofugic group which can be split off in position 4, or

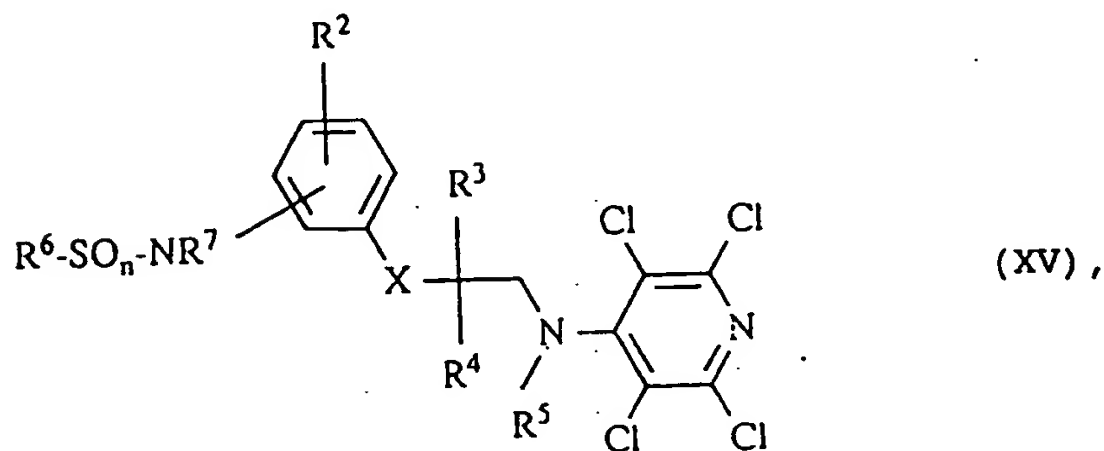
c) from a compound of the general formula XII



in which  $R^2$ - $R^5$  and X have the given meanings and  $R^{1'}$  has the same meaning as  $R^1$  or from a compound of the general formula XIV



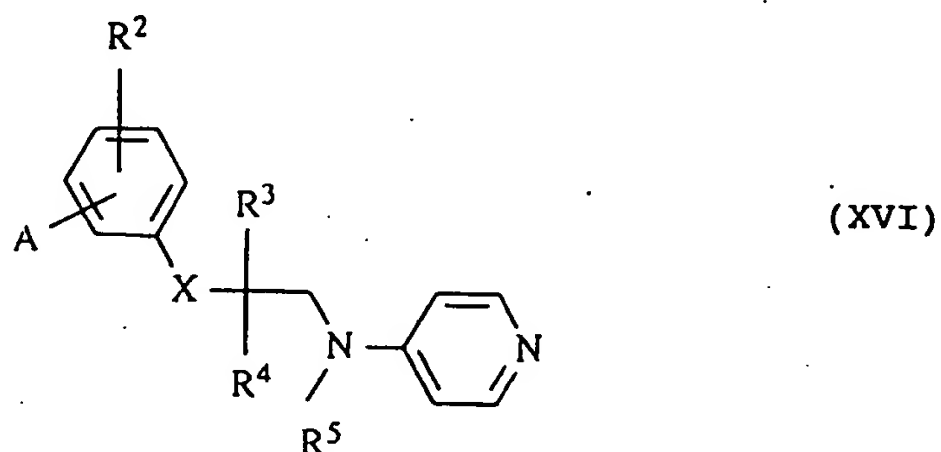
in which  $R^2$ - $R^6$  and X have the given meanings, n is 1 or 2 and X' signifies oxygen or the imino group NH, or from a compound of the general formula XV



in which  $R^2$ - $R^6$  and X have the given meanings and  $R^{7'}$  has the same meaning as  $R^7$  with the exception of the hydrogen atom, removes the chlorine atoms of the pyridine ring by catalytic hydrogenation, and subsequently possibly converts the compounds obtained into physiologically compatible salts, hydrates, solvates or optical isomers.

13. Process for the production of compounds of the general formula I as claimed in claim 1, wherein  $R^1$  in the general formula I denotes a  $R^6$ -SO-NR<sup>7</sup>-,  $R^6$ -SO<sub>2</sub>-NR<sup>7</sup>-,  $R^6$ -SO-O- or  $R^6$ -SO<sub>2</sub>-O- group,

wherein compounds of the general formula XVI

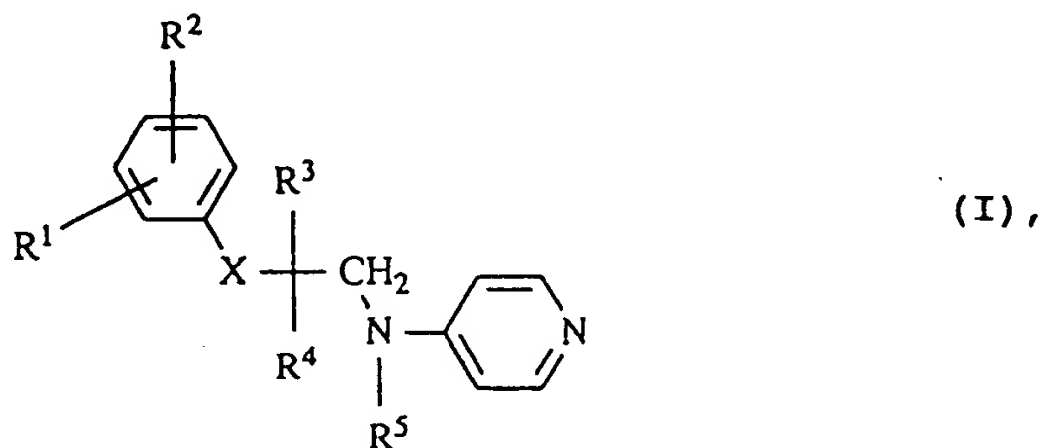


in which  $R^2$ - $R^5$  and X have the stated meanings and A denotes a hydroxy group or an amino group  $-NHR^7$ , is reacted with a sulfinyl chloride  $R^6-SOCl$  or a sulfonyl chloride  $R^6-SO_2-Cl$  in which  $R^6$  and  $R^7$  have the stated meanings.

14. Pharmaceutical agents containing at least one compound of formula I as claimed in one of the claims 1 to 11 in addition to pharmaceutical carrier and auxiliary substances.
15. Use of compounds of formula I as claimed in one of the claims 1 to 11 for the production of pharmaceutical agents for the treatment of thromboembolic diseases.

A b s t r a c t

The invention concerns new 4-aminopyridines of the general formula I



in which

- $R^1$  denotes a  $R^6$ -SO-NR<sup>7</sup>-,  $R^6$ -SO<sub>2</sub>-NR<sup>7</sup>-,  $R^6$ -NR<sup>7</sup>-SO-,  $R^6$ -NR<sup>7</sup>-SO<sub>2</sub>-,  $R^6$ -SO-O-,  $R^6$ -SO<sub>2</sub>-O-,  $R^6$ -O-SO- or  $R^6$ -O-SO<sub>2</sub>- group,
- $R^2$  denotes a hydrogen or halogen atom, a cyano, alkyl, alkoxy or haloalkyl group,
- X denotes an oxygen atom, a sulphur atom or a NH group,
- $R^3$  and  $R^4$  are the same or different and denote hydrogen atoms or alkyl groups,
- $R^5$  denotes a hydrogen atom, an alkyl group or an aralkyl group,

- $R^6$  denotes an aliphatic or cyclic residue which is substituted if desired,
- $R^7$  denotes a hydrogen atom, or an aliphatic or cyclic residue which is substituted if desired,
- Y denotes a linear or branched alkylene chain,
- $R^8$  and  $R^9$  are the same or different and denote hydrogen atoms, aralkyl, cycloalkyl or alkyl groups which can be substituted once or several times by halogen, hydroxy, alkoxy, alkylcarbonyloxy, amine or carboxy, or  $R^8$  and  $R^9$  together with the N atom to which they are bound, form a saturated ring which can contain an additional oxygen, sulphur or nitrogen atom,

as well as hydrates, solvates and physiologically tolerated salts thereof. The invention also concerns the optically active forms, racemates and mixtures of diastereomers of these compounds.

The invention also concerns processes for the production of the above compounds, pharmaceutical agents which contain such compounds as well as the use of these compounds in the production of pharmaceutical agents.